Title: Insomnia Self-Management in Heart Failure

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SPECIFIC AIMS

Almost 75% of HF patients, a population of over 5 million Americans[1] who have poor function and high levels of morbidity and mortality, report poor sleep.[2-7] As many as 25-56%[5,8-10] of HF patients report comorbid chronic insomnia (difficulty initiating or maintaining sleep or waking early in the morning, with non-restorative sleep that persists for at least a month). Chronic insomnia may contribute to the development of HF[11] and incident mortality[11,12] and is associated with disabling symptoms (fatigue, dyspnea, anxiety, depression, excessive daytime sleepiness, and pain)[4,6,8,10,13-18] and decrements in functional performance.[19]

Despite the importance of insomnia to critical HF outcomes, HF patients report that health care professionals fail to address it.[20] Patients prefer behavioral approaches to hypnotic medications[20] that are associated with adverse events, such as daytime sleepiness, falls, and altered cognition. Yet, little is known about the effects of behavioral treatment for chronic insomnia among HF patients who are especially vulnerable to high symptom burden and other negative outcomes.

Cognitive behavioral therapy for insomnia (CBT-I), a self-management intervention, focuses on dysfunctional behaviors and cognitions that perpetuate physical and psychological arousal[21-23] and chronic insomnia.[24] The effects of CBT-I are more durable than hypnotic medications[24-26] without negative daytime effects.[27] In our pilot randomized controlled trial (RCT), CBT-I improved chronic insomnia, sleep quality, actigraph-recorded 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.[28] Both groups had stable HF at baseline and received evidence-based HF disease management. At six months after treatment, the effects on insomnia were sustained in the CBT-I group, with large improvements in fatigue and anxiety over baseline and first follow-up and improvement in depression, after controlling for baseline symptoms and clinical/demographic characteristics.[29] These improvements contrasted with worsening fatigue, smaller decreases in insomnia, and no change in anxiety or depression in the attention control group. Insomnia remission was associated with mild vs. moderate-severe symptom clusters and functional performance.

Evidence that chronic insomnia predicts incident HF and mortality[11,12] and trends suggesting reduced hospitalization among HF patients who received CBT-I in our work suggest the potential benefits of CBT-I to health care utilization and event free survival - outcomes of critical importance to HF patients that have not been examined in relation to CBT-I. Building on these promising results, the purposes of the proposed RCT are 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 health care utilization over twelve months among patients who have stable chronic HF and comorbid chronic insomnia. We will also explore the effects of CBT-I on event-free survival.

We will address the following specific aims (*primary outcomes): (1) Test the sustained effects (baseline, 3 months (2 weeks post intervention), 6 and 12 months) of CBT-I provided in 4 group sessions over 8 weeks, compared with HF self-management education (attention control condition), on: (1a) *insomnia severity and self-reported and 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 (PVT); and (1c) symptom clusters [membership in clusters characterized by severity of specific symptoms; transition between clusters over time]; (2) Test the sustained effects of CBT-I on self-reported and objective functional performance; and (3) Examine the cost-effectiveness of CBT-I. Exploratory aim: We will explore the effects of CBT-I on event-free survival.

Hypotheses: CBT-I, compared with an attention-control condition (HF self-management education), leads to: (1a) decreased insomnia severity and sleep latency and increased sleep quality, duration and efficiency that are sustained at 6, and 12 months; (1b) decreases in severity of symptoms and improvements in psychomotor vigilance that are sustained at 6, and 12 months; and 1c) transition between symptom clusters that have higher symptom severity to those that have lower symptom severity over time. (2) CBT-I will lead to increased self-reported and objective functional performance; (3) CBT-I is cost-effective, compared with HF self-management education alone.

Support for the proposed hypotheses will lead to future research focused on the dissemination and translation of CBT-I into diverse HF settings. Increased access to CBT-I has high potential to improve HF patients' ability to self-manage sleep and daytime symptoms and decrease the costs of health care resource utilization.

RESEARCH STRATEGY

Significance. This study is responsive to PA 14-344 "Self Management for Health in Chronic Conditions" and NINR's strategic plan.[30] Our study will address the dearth of efficacious self-management interventions for patients who have co-occurring conditions, specifically comorbid chronic insomnia and HF.

Insomnia occurs in 25-56% of patients with HF,[4,5,7-9] a population of over 5 million in the U.S.,[1] who suffer from high symptom burden, poor function, morbidity, mortality and excessive health care resource utilization. Insomnia is more common in HF patients than "healthy" controls[7] and the general population.[31] It is distressing[6,20] and associated with symptoms (fatigue, depression, dyspnea, anxiety, pain, sleepiness)[4,8,13,17,18] that decrease quality of life[5,20] and functional performance,[8] "the day to day corporeal activities people do in the normal course of their lives to meet basic needs, fulfill usual roles, and maintain health and wellbeing."[32,p.198] HF patients think insomnia is critical to daytime function, but clinicians fail to address it.[20]

Influences on symptoms and function are multifactorial in HF[33,34] and include insomnia. For example, 51% of patients with stable chronic HF and evidence-based HF disease management[35] had chronic insomnia that was not explained by HF severity, comorbidity, or sleep apnea (SA). Insomnia was related to depression, fatigue, sleepiness (all $p < .05$) and function, including a 100-foot decrement in 6 minute walk (6MW) distance ($p < .001$), after controlling for demographics, comorbidity and left ventricular ejection fraction (LVEF).[8]

Chronic insomnia predicted incident HF [HR (hazard ratio) = 0.95 (CI95: 0.55 -1.62)] for one insomnia symptom to HR= 5.25 (CI95: 2.25 - 12.22) for 3 symptoms, after controlling for clinical/demographics over a mean 11 year follow-up (p for trend = .0010) and had a dose-dependent relationship HF mortality.[11] These findings confirm and extend earlier studies.[12] Associations between insomnia-related outcomes (e.g., depression,[36-38] fatigue,[39] symptom clusters,[13,20,39,40] function[8]), hospitalization, death, and event-free survival (EFS)[5] emphasize the importance of insomnia and the potential benefits of treating this comorbid condition.

Chronic hyper-arousal, with increased sympathetic and HPA axis activation[11,12] may explain the relationships between insomnia and EFS. Associations between day/night urinary epinephrine ratio and wake after sleep onset ($r = -0.53$, $p < .01$); day/night urinary cortisol ratio, sleep quality ($r = 0.39$, $p = .04$) and fatigue ($r = -0.54$, $p = .0007$)[41] in HF patients partially support this explanation. The proposed RCT will contribute to understanding the causal relationships between insomnia and EFS, a critical outcome.

Evidence-based HF disease management and self-care/self-management are standard elements of HF care, but typically do not address comorbid conditions (i.e. chronic insomnia) or focus on ameliorating thoughts and behaviors that contribute to insomnia.[42,43] Cognitive behavioral therapy for insomnia (CBT-I), a multi-modal self-management intervention, addresses dysfunctional behaviors and cognitions that perpetuate psychological/biological arousal[22] and chronic insomnia.[24] CBT-I effects are more durable than hypnotic medications[24-26] without negative daytime effects.[27] Our pilot RCT[28,44] included adults with stable HF, chronic insomnia, and evidence-based HF management.[35] It revealed large short-term and sustained CBT-I effects on insomnia severity and fatigue and improvements in anxiety and depression, symptoms common to both HF and insomnia,[45] at six months, compared to the attention control group (HF self-management education[46]) who had less improvement, worsening, or no change. These findings are especially notable, given the frequent refractory nature of HF symptoms, especially fatigue, and the dearth of available symptom management interventions. The associations of mild vs. moderate/severe symptom clusters with insomnia remission underscore the potential benefits of the effects of CBT-I on symptom clusters (patterns of severity of 2 or more symptoms) and our plan to examine CBT-I effects on symptom clusters better captures the clustered nature of symptoms occurring in real life[13,15,47] than past studies of isolated symptoms.

We will add to CBT-I and self-management science by testing the effects of CBT-I on objective and clinically relevant outcomes.[48] Use of the psychomotor vigilance test (PVT),[49,50] a measure of the neurobiological effects of sleep loss and the PROMIS brief sleep impairment items[51] will increase understanding of HF patients' reported low levels of sleepiness[8,52,53] that may reflect failure to recognize sleep loss, lack of sensitivity of the Epworth scale, and/or high levels of arousal.[54] The 6 minute walk (6MW), a prognostic measure,[55,56] will extend self-report. Use of legacy measures of sleep/sleepiness and PROMIS addresses the need to use common data elements in symptom science[57] and will enable comparability with both past and emerging studies.

Cost-effectiveness analysis (CEA) will address a gap in self-management and CBT-I science,[48] as few, if any, studies have addressed it. Promising effects of CBT-I on hospitalization, accounting for 75% of HF costs,[13,58] suggest its benefits to health care resource utilization, a critical outcome due to the $32 billion costs of HF that will rise to $70 billion in 2030.[1] High health care resource utilization[59-63] and indirect costs (e.g., productivity)[64] of insomnia[13] underscore the need for CEA. Risk of death from HF associated with insomnia[11] and associations between insomnia remission and hospitalization (pilot work) emphasize the need to explore CBT-I effects on EFS.

The results of this study will support future studies of the effectiveness[65] and sustainability of CBT-I in diverse HF disease management settings (e.g., cardiac rehabilitation, HF support groups). Future delivery modes may include interactive www, mobile "apps," telehealth modalities, or other approaches and will extend the reach of the intervention to enable improvement of insomnia and related symptoms in many settings.

Innovation. The primary innovations include: (1) use of a CBT-I to improve chronic insomnia, symptoms, and functional performance among patients with comorbid insomnia and HF; (2) the plan to test the effects of CBT-I on symptom clusters and functional performance, in contrast to previous CBT-I studies that evaluated isolated symptoms and broad quality of life outcomes; (3) use of objective measures of the neurobiological effects of chronic sleep loss and functional performance as outcomes of CBT-I; (4) evaluation of direct and indirect costs of chronic insomnia treatment in HF; (5) use of latent cluster and latent transition analysis to evaluate the effects of CBT-I on symptom clusters; and (6) exploration of the effects of CBT-I on event-free survival (EFS). To our knowledge, no investigators have conducted a fully powered RCTs of CBT-I among HF patients, and few, if any RCTs evaluated the effects of CBT-I on symptom clusters, EFS, or health care resource utilization.

The organizing framework is based on chronobiologic and homeostatic models of sleep regulation, the "3-p" model of insomnia,[66-68] the Framework for Self- and Family Management of Chronic Conditions,[69,70] and research on symptoms/symptom clusters. Sleep is "characterized by reduced awareness of and interaction with the environment, lowered motility, and partial or complete abeyance of voluntary behavior and consciousness."[71] Chronic insomnia, a sleep disorder, occurs ≥ 3 nights/week for ≥ a month,[5,8-10] with adequate sleep opportunity, non-restorative sleep and difficulty initiating sleep, maintaining sleep, and/or waking too early.[72] It is comorbid when it occurs with, but is not explained by, psychiatric or medical disorders (e.g., HF)[72] and persists with optimal treatment of the comorbid condition.[42,43] The 3-p model posits that biological, psychological, and social traits (predisposing factors); acute triggers (i.e. 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 physiological and biological arousal[67] (broken boxes, Fig. 1). Common perpetuating factors lead to somatic and/or psychological arousal – the "final common pathway"[42,p.560] to chronic insomnia.

Predisposing and precipitating factors are poorly understood,[68] but multi-factorial.[73] Aging and gender often predispose to insomnia, but age, gender,[5,7-9] left ventricular ejection fraction (LVEF),[7,9,73] cardiac medications,[9,74] and sleep apnea (SA) were not related to chronic insomnia in HF.[3,8] Comorbidity was related to chronic insomnia,[75] but associations with NY Heart Class are conflicting.[8] However, because these factors may contribute to insomnia and other study outcomes, they will be explored as possible covariates. (Fig. 1).

HF patients reported perpetuating factors for insomnia. They attributed awakening to modifiable factors (e.g., increased time in bed awake,[7] insufficient sleep,[5] frequent napping,[5,7,9] use of TV as white noise at night[76]). Negative associations between sleep hygiene and sleep quality[3] and positive associations between insomnia severity and dysfunctional beliefs and attitudes about sleep, mental anxiety, and sleep effort (all $p < .05$)[76] underscore the contributions of perpetuating factors to chronic insomnia among HF patients.

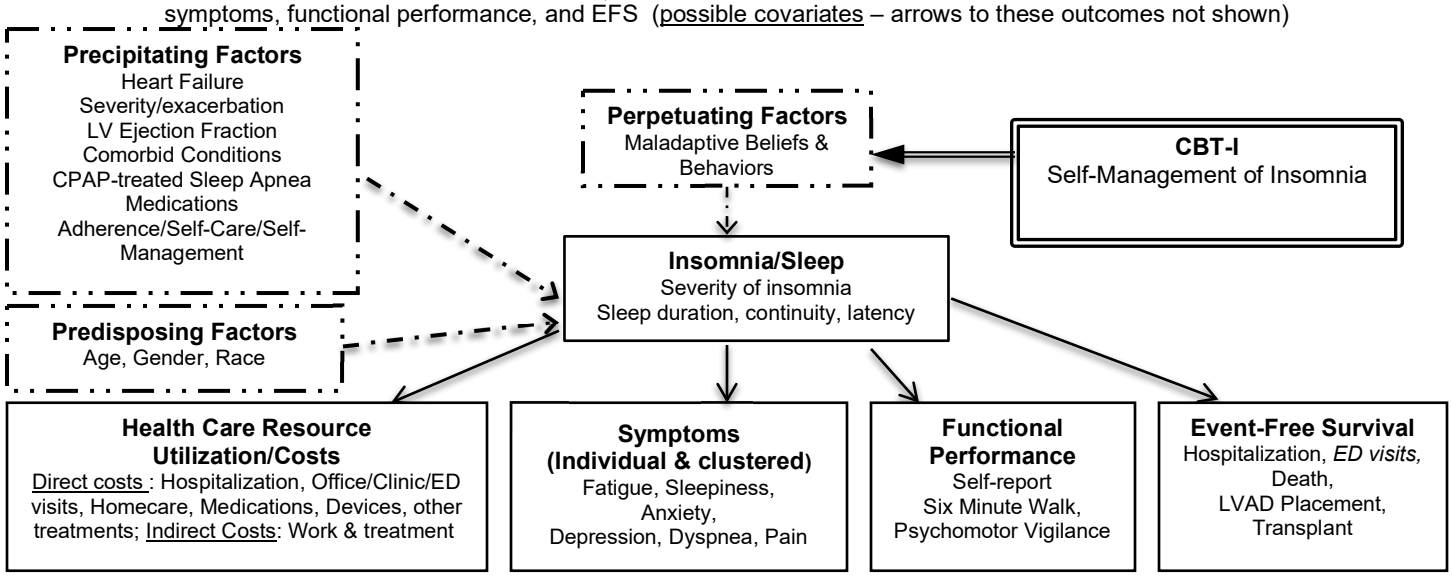
Self-management (knowledge and skills to manage chronic conditions and related emotions and symptoms)[69,70] is the conceptual basis for CBT-I and the attention control condition (HF self-management education). CBT-I includes cognitive and behavioral strategies that address perpetuating factors for insomnia (Table 1, Fig. 1). HF self-management[46] includes behaviors needed to manage HF itself. Although self-care/self-care management[77] and symptom clusters[13] were associated with EFS in observational studies, outcomes of self-management interventions, such as health care resource utilization, are inconsistent.[46,78] The effects of CBT-I vs. HF self-management education will be compared in the proposed study.

CBT-I protocols vary in group/individual format, some elements, and session frequency, but address perpetuating factors through behavioral (stimulus control, sleep restriction therapy, relaxation training), cognitive (cognitive therapy), and educational (sleep hygiene) elements.[24] Stimulus control includes re-associating the bed with sleep; maintaining a consistent sleep/wake schedule; going to bed only when sleepy; getting out of bed when unable to sleep; using bed only for sleep and sex; and avoiding naps.[24] Sleep restriction limits time in bed to actual sleep time. With therapist supervision, patients decrease time in bed to maximize sleep efficiency and then gradually increase it until they optimum efficiency and duration. Cognitive therapy clarifies misperceptions and misattributions about insomnia and sleep, reframes unrealistic expectations, reduces performance anxiety, and increases control over sleep.[24,79] Relaxation therapy reduces somatic and cognitive arousal. Sleep hygiene focuses on lifestyle and environment,[24] but is not efficacious alone.[24,80] Hypnotic tapering is efficacious when provided gradually with provider supervision.[81,82]

CBT-I has consistent effects on chronic insomnia[28,42,83,84] and sleep efficiency,[28,85-100] and improved some symptoms in non-HF groups. Detection of large effects of CBT-I on insomnia severity and fatigue[28] and associations between symptom clusters, insomnia remission and functional performance among HF patients (Fig 1, Table 2) extends past CBT-I trials in other groups to a group who is especially vulnerable to symptom burden. Both symptom clusters[13] and insomnia contribute to event-free survival (EFS),[11] health care resource utilization, and indirect costs.[60,101] We will examine the effects of CBT-I on these important HF outcomes, while considering possible covariates (Fig. 1).

Fig. 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 EFS (possible covariates – arrows to these outcomes not shown)



Preliminary Studies. Redeker, PI, conducted studies of sleep, symptoms, and functional performance among adults with heart disease for over 20 years and has ongoing collaborations with the study team. Studies characterizing sleep and sleep disorders in HF; contributors to chronic insomnia; associations between insomnia, sleep, symptoms, and functional performance; HF patients' perceptions of sleep; and the feasibility and preliminary efficacy of CBT-I in HF are summarized below.

HF patients have poor sleep and insomnia. Our study, funded by the American Heart Association,[7] revealed poorer self-reported and objective sleep quality, latency and wake after sleep onset, ($p < 0.05$), but no different sleep duration in stable HF patients (M age = 59.10±13.04 years; n = 20/33.9% women; n = 15/26% Black; n = 5/8.5% Hispanic), than "healthy" adults (M age = 55.00 ± 10.29 years; n = 30/50% women; 79% white). In another study (R01NR008022), 51% of 173 stable HF patients from HF disease management programs (M age = 60.35 ± 16.1 years/n = 60/35% women; n = 110/59% white; n = 50/29% Black, n = 10/5.7% Hispanic) had one or more chronic insomnia symptoms: difficulty falling asleep (n = 71/42%), staying asleep (n = 62/36%), or waking too early (n = 41/25%).[8] Sleep apnea (SA),[53] ejection fraction (LVEF), comorbidity, and NY Heart Class did not differ between patients with/without chronic insomnia,[8] but insomnia was negatively related to polysomnographic sleep duration ($p < .01$) and efficiency ($p < .05$).[8]

Sleep disturbance/insomnia are associated with symptoms and function in cardiac surgical[102,103] and HF patients.[10,19] Wake time and sleep quality explained 11-21% of the variance in 6 minute walk (6MW), daytime activity, and self-reported physical function in stable HF patients (all $p < .05$),[19] controlling for LVEF and NY Heart class. Chronic insomnia was associated with physical function (SF36) ($p < .001$), fatigue ($p < .001$), depression, ($p < .001$), sleepiness ($p = .013$)[8] and pain ($p < .001$); and shorter 6MW in people with insomnia [M = 875.3 feet (CI95 = 791.0, 959.6)] vs. no insomnia [M = 976.8, (CI95 = 882.9, 1070.7)][8] (R01NR008022).

Insomnia is important to HF patients. Stable HF patients (N = 11, M age = 73 years, 5 women) described critical effects of chronic insomnia on function and mood; unpredictability of a good night's sleep; need to catch up with naps; and clinicians' failure to attend to sleep. Dislike of hypnotics, interest in behavioral treatment, and modifiable perpetuating factors (pain, frequent urination, discomfort while side-lying due to defibrillator, worries, poor sleep hygiene: use of TV as a sleep aid), with some use of sleep-promoting behaviors (e.g., music, white noise) indicate the importance of behavioral treatment (P30NR008999).[20]

CBT-I is feasible and acceptable. We evaluated the effects of CBT-I ("Healthy Sleep:" HS), compared with an attention-control [HF self-management education ("Healthy Hearts:" HH)] on insomnia severity, symptoms, and functional performance among HF patients in a pilot RCT (R21NR011387).[28] (Table 1). Both conditions

included 4 bi-weekly group sessions with phone follow-up on intervening weeks (total = 8 weeks), followed treatment and treatment fidelity protocols, and included guides/workbooks (Appendix). Participants had Class II-III HF, were stable at recruitment (no hospitalizations, ED visits, or titration of vasoactive medications in past

Table 1. 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 in 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 contact form
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: Fluid and sodium Management; Effective communication w/ healthcare providers
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; OTC medications/herbal remedies; Cardiac devices
Week 7: Session 4	Reinforce adherence/Call attention to progress/review; Relapse prevention advice *Telephone calls weeks 2, 4, 6, 8	Healthy Lifestyle: Diet: Lipids, sodium, Calories; CVD risk factors; Stress Management/relaxation; Exercise; Environment and sleep; Review

Month), had standard evidence-based HF disease management;[35] concerns about insomnia for ≥ one month; scored ≥ 8 on the Insomnia Severity Index,[104] and had no-mild untreated SA or were adherent to SA treatment. We randomized to HH or HS in groups of 5, obtained self-reports of insomnia/sleep, symptoms and functional performance and 2 weeks of wrist actigraphy/diaries; provided HS/HH interventions; and repeated full assessment at 2 weeks post-intervention (T1). Self-report measures included the Insomnia Severity Index, Pittsburgh Sleep Quality Index, Centers for the Epidemiological Studies of Depression Scale, Spielberger State Anxiety Scale, SF-36 Pain Scale, Multi-dimensional Assessment of Fatigue Scale, and the SF-36 Physical Function Component. With the exception of actigraphy (not collected due to budget), these measures, and hospitalization were assessed at T2 (6 months). Hospitalization was also elicited at 12 months.

We enrolled 52 patients (planned n = 40); 48 completed treatment/follow-up in HS (n = 29) or HH groups (n = 19).[28] One HS patient did not complete due to a heart transplant. In the HH, non-completion was due to disappointment with randomization (n=1); loss to followup (n=1); and change to shift work (n=1). Eighty-eight percent of completers had 100% attendance. Inclement weather, damage to home, and death in family and were reasons for missed sessions that were made up by phone. Completers included 23 (47.9%) women, 15 (32.1%) African Americans, and 32 (66.7%) Whites and had NY Heart Class II or III HF. Age was M = 61.9 ±13.3 (HS group) and 55.2 ±16.2 years (HH group) (p =.12). There were no statistically significant group differences at baseline on gender, NY Heart Class, comorbidity, symptoms or function. The apnea hypopnea index was M = 7.44 ± 5.5 in participants not in treatment for SA. The proportion of patients using positive airway pressure (PAP) was equivalent between groups [n = 5 (17%) (HS) and n = 3 (16%) (HH)]. OTC or prescribed hypnotics were used 3 or more times/week by n = 7 (24%) (HS) and n = 7 (37%) (HH); 72% used ACEI/ARBs and 92% used beta-blockers, but there was no statistically significant difference between groups.

Satisfaction and acceptability were high and averaged 7.5-8.7 (scale: 0-10/10= high). Both groups rated scheduling, location, payment, study materials, interventionist effectiveness, and willingness to continue treatment as 8.5-9.5. There were no statistically significant differences between groups on ratings, and participants had no difficulty completing the measures. PAP users reported that CBT-I was helpful.

CBT-I had early and sustained effects. Insomnia severity improved in both groups (T1) and was similar to T1 at T2 (Table 2). The CBT-I effect was moderate-large at T1, with the mean decrease of > 7 points exceeding the criterion for improved function,[105] while the HH decrease was much smaller. In the HS, 93% improved across one or more levels of insomnia severity and only 2 deteriorated, while 68% of the HH group improved, and 26% deteriorated. At T1, only 48% of the HS had any insomnia (ISI ≥ 8), compared with 68% of the HH group [OR=0.43, CI95=0.13,1.45]. The HS group improved at T1 on sleep quality, compared with HH. Self-reported (PSQI) and actigraph SE improved more at T1 in HS, and PSQI SE was similar at T2.

We found moderate-large reductions in fatigue at T1 in HS ($p < .01$)[28] (Table 2). The HS group continued reductions in fatigue at T2 ($p < .01$) (large effect), with no additional intervention, while fatigue increased in HH. There were no statistically significant differences in improvements in anxiety or depression at T1; but large improvements in anxiety in HS at T2 (effect size = 0.69, $p < .01$). Depression continued to improve in HS at T2,

but not HH. The CBT-I effect on depression was significant when adjusted for insomnia remission (p = .02). Pain did not improve, but was correlated with insomnia severity (p < .01), fatigue (p = .02), sleepiness (p = .07), and physical function (p < .01). Sleepiness was low in both groups (range 6.84-7.55), consistent with past research,[53] and may reflect sympathetic activation,[54] lack of recognition of sleepiness or insufficient sensitivity of the Epworth Scale. CBT-I effects on sleepiness will be evaluated with additional measures in this study.

Cluster analysis performed on symptom severity at T1 (pain, anxiety, depression, fatigue, dyspnea sleepiness) revealed 3 clusters: I (all mild: N = 25), II (high pain/dyspnea: N = 9), III (high depression, anxiety, sleepiness: N = 14). Of those in insomnia remission at T1 (ISI < 8), 65% were in Cluster I, and only 10% were in Cluster III, while 42.3% of those with persistent insomnia were in Cluster III (p = .054). Functional performance was higher in Cluster I than II or III (p < .0001). These associations suggest the significance of our plan to examine the effects of CBT-I on changes in symptom cluster group membership.

After controlling for baseline symptoms, the estimated incidence rates of cardiac hospitalizations in one year were 11.7% and 18.7% in HS and HH, respectively; 9% of those with insomnia remission, compared with 27.8% with persistent insomnia were hospitalized. Taken together with fewer cardiac hospitalizations in those with mild symptom clusters vs. more severe clusters (Cluster I: 4.8%; Clusters II/III: 35%), these data suggest the greater benefits of CBT-I, compared with self-management education, to health care resource utilization.

Summary. We documented the high prevalence of chronic insomnia and its associations with disabling symptoms and functional performance in patients with stable HF and evidence-based HF disease management. Our pilot RCT revealed clinically and statistically significant early effects of CBT-I, a self-management intervention, compared with HF self-management education, on chronic insomnia, SE, and fatigue, while controlling for covariates. High acceptability and attendance, sustained effects, completion of all measures without burden, and promising effects on hospitalization are strong evidence of the impact of CBT-I on critical HF outcomes and the feasibility of our approach. The proposed fully powered RCT will establish a strong foundation for future research, including dissemination of CBT-I into HF disease management settings.

Table 2. Means, Standard deviations and Effect Sizes for Selected Outcomes at 2 Weeks (T1) & 6 Months (T2)

Variable	GROUP	Pre (T0)	Post (T1)		Post (T2)	
		M (SD)	M (SD)	ES#	M (SD)	ES#
Insomnia Severity	CBT-I (HS)	15.38 (4.79)	7.76 (5.21)	0.65	8.39 (4.44)	0.65
	Att Control (HH)	14.00 (4.33)	10.32 (5.30)		10.00 (4.34)	
Sleep Quality: PSQI *	CBT-I (HS)	9.43 (3.37)	7.25 (3.19)	0.46	7.65 (3.20)	0.02
	Att Control (HH)	9.78 (3.84)	9.32 (3.16)		7.77 (4.64)	
Slp Efficiency (%): (PSQI)	CBT-I (HS)	76.64 (15.78)	82.44 (14.45)	0.38	79.51 (18.74)	0.01
	Att Control (HH)	73.95 (14.18)	73.89 (11.81)		74.16 (18.95)	
Slp Efficiency (%) Actigraph $	CBT-I (HS)	72.62 (10.25)	75.92 (8.35)	0.70	NA $	NA
	Att Control (HH)	77.35 (7.09)	76.07 (11.03)		NA $	
Fatigue	CBT-I (HS)	27.49 (13.16)	21.49 (10.61)	0.64	20.13 (11.52)	1.22
	Att Control (HH)	23.90 (11.20)	24.45 (10.00)		27.64 (10.43)	
Depression	CBT-I (HS)	13.76 (9.18)	12.17 (10.56)	0.06	8.87 (5.98)	0.16
	Att Control (HH)	16.74 (10.54)	14.63 (8.63)	(**)	14.00 (7.99)	
Anxiety	CBT-I (HS)	35.93 (11.61)	34.55 (13.73)	0.12	30.17 (9.29)	0.69
	Att Control (HH)	38.32 (13.68)	38.05 (10.73)		37.23 (12.69)	
SF36 Physical Function	CBT-I (HS)	26.72 (2.04)	27.21 (2.01)	0.26	26.96 (2.14)	0.23
	Att Control (HH)	27.11 (2.07)	27.30 (2.28)		27.82 (2.23)	

*higher score = poorer sleep quality; **favors attention-control group. ES# effect size; *$actigraph data not collected at T2; PSQI = Pittsburgh Sleep Quality Index*.

APPROACH

Design. We will conduct a 2-group randomized controlled trial (RCT). Participants will complete baseline and be randomized to CBT-I (4 bi-weekly group sessions/8 weeks: "Healthy Sleep:" HS) or attention control (HF self-management education: "Healthy Hearts:" HH) (Table 1). We will measure sleep, sleep-related impairment, psychomotor vigilance, symptoms, self-reported and objective functional performance and cost-effectiveness at baseline (BL) and follow-up (F/U) (wks 2; months 6, , and 12), time frames selected due to the dynamic nature of HF severity and symptoms; and track event free survival (EFS) through the first half of year 5 of the study, allowing a range of 18-45 months of follow-up, based on enrollment times.

The sample will include individuals ≥ 18 years of age with NY Heart Class II-III HF who are cognitively intact (clinical impression), speak/read English, concerned about sleep for ≥ 1 month, and score ≥ 8 on the Insomnia Severity Index,[104] an indicator of ICSD-2 insomnia.[106] Participants will have preserved (LVEF > 45%) or

reduced systolic function (LVEF ≤ 45%). LVEF was not associated with chronic insomnia,[8] but may contribute. HF patients at the planned sites undergo echocardiography annually and with cardiac changes. We will use the most current LVEF. Sleep continuity is negatively related to age, but we will include adults of all ages due to the greater effects of insomnia on fatigue in younger adults.[8] Participants will receive HF care per AHA/ACCF guidelines,[35] consistent with practices in the clinical recruitment sites.

Depressive symptoms are common in HF[10] and often comorbid with insomnia. CBT-I improves depression,[98,107,108] including suicidal ideation.[109] Antidepressants[94] and depression did not diminish its effects. We will include patients with no/moderate depression and those on anti-depressant, anxiolytic and/or hypnotic medications. Hypnotic tapering is an effective part of CBT-I,[81,82] and will be an option, but not required.

Exclusion criteria are untreated restless legs syndrome; night/rotating shift work; travel across 2 or more time zones within one month of enrollment; contraindications to sleep restriction [seizure disorder, severe sleepiness (Epworth Scale >18), bipolar disorder]; neurological/musculoskeletal conditions affecting the non-dominant arm (use of wrist actigraph), active illicit drug use, dementia, and end-stage renal failure. Participants who are hospitalized or have emergency department visits, unstable conditions, or changes in vasoactive medications within 4 weeks of recruitment will not be enrolled until 4 weeks elapse without new events. Patients with these events after enrollment will be retained; events will be tracked and included in analyses.

Chronic insomnia and sleep apnea (SA) are often comorbid with HF,[110-112] but SA was not associated with insomnia in HF patients[3,8] and did not affect CBT-I outcomes in older adults.[94] Although positive pressure (PAP) improves some cardiac variables, lack of rigorous long term RCTs preclude widespread SA treatment in HF,[113] and the lower treatment threshold is not well defined.[113-115] Most studies were small, poorly controlled, and included patients with moderate-severe SA (apnea hypopnea index/AHI ≥ 15).[115] One study (n = 40 completers)[116] had participants with AHI > 5, but mean AHI was ~ 28, and the proportion with mild SA was not reported. Given limited evidence of PAP benefits in very mild SA, we will include patients with AHI < 10 and refer those with AHI ≥ 10 for further evaluation. Participants with significant SA will be eligible If adherent to PAP ≥ 6 hours/night for at least 3 months. Titration of PAP or sleep studies with PAP use are beyond the study scope, but participants will be eligible if they have insomnia once adherent to PAP. The proportion of PAP users was equivalent between groups in our pilot.

We will track clinical/demographic characteristics [age, gender, race, SA, depression, hypnotics, HF medications (ACEI/ARB, beta blockers), LVEF, NY heart class] and relevant changes at all study milestones and include these indicators in relevant analyses (See data analysis).

Sample Size. We performed power analyses to detect the effects of CBT-I on primary outcomes [insomnia severity, sleep quality (PSQI), self-reported (PSQI) and actigraph sleep efficiency (SE), and fatigue] with pilot data in which we randomized HF patients to CBT-I (HS) or attention control (HH). We calculated powers to detect differences in changes in outcomes from BL between the two groups to post-intervention (2 wks/T1) with 5% type I error.[117] We also calculated powers with scenarios of high within-subjects correlations (Rho=0.6, 0.7, 0.8) for repeated measures during F/U (2 wks, 6, , 12 months) by assuming consistent effect sizes over time[118] (Table 3). A sample of 100 independent participants per group will yield > 90% power to detect CBT-I effects on insomnia severity (ES=0.65), fatigue (ES=0.64), and PSQI sleep quality (ES=0.46) and power of 76.6% for PSQI SE (ES=0.38), but a power of 99.9% for actigraph-measured SE (ES=0.70). In scenarios based on within-subjects correlations of outcomes, we anticipate > 95% power for most outcomes and > 80% power for self-reported SE. Inclusion of 200 subjects (100/group) will permit sufficient power to detect the association between improved insomnia severity and symptoms [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 will randomly assign 200 participants in 25-33 clusters of 6-8. Because we do not expect dependency among participants in the same clusters, we will not increase the sample for random cluster assignment.

We computed the power for estimating cost-effectiveness with Willan[119] and Glick's[120] 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 QALYs of -0.1, and willingness-to-pay of $50,000 per QALY. The expected difference in QALYs, based on the pilot study, 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.

Setting/Recruitment. We will recruit from the Yale-New Haven Hospital (YNHH) HF Center and the VA CT System. Dr. Jacoby will facilitate recruitment at YNHH, and Dr. Yaggi will refer from the VA where he directs the sleep clinic and conducts research on sleep in CVD. YNHH and the VA follow ~ 4000 HF patients. Because Yale cardiologists practice in both sites with AHA/ACCF guidelines,[35] HF management is comparable. Based on our pilot, about 55% of screened patients will have chronic insomnia, of whom 50% will

meet all criteria, and 85-90% will consent. We expect to enroll ~ 23-25% of screened patients, a large number, given the prevalence of HF. Likely exclusions will be untreated SA; unstable HF, medical or psychiatric status; and cognitive dysfunction. Lack of interest, session frequency, or travel distance may result in refusal. We had 92% completion in our pilot, but will recruit an additional 20% (total N = 240) to address potential attrition.

We will obtain IRB approval, and HF clinicians will identify consecutive potential participants by eliciting concerns about sleep; explain the study; and obtain agreement for contact. We will promote the study with brochures in waiting areas and the Yale CTSA website. The research assistant (RA) will meet with interested patients, explain the study, answer questions, and obtain informed consent and a HIPAA waiver for medical record review and further screening. The RA will screen patients for health/sleep history, including other sleep disorders, and depression (PHQ-9[121 121]). She/he will screen those with PHQ-9 scores ≥ 15 (moderately severe-severe) with the Structured Clinical Interview for DSM-IV Axis Disorders[122] (See inclusion/exclusions).

We will also recruit at the Yale Sleep Medicine Clinic. Participants will be recruited from among those patients seen at the Yale Sleep Medicine clinics who carry a diagnosis of chronic HF. The research assistant and program manager will work with Dr. Yaggi to identity such patients in clinic medical records. Medical records will be screened to determine if prescreening criteria are met: >18 years of age; physician diagnosis of stable heart failure, New York Heart Class II-III Heart Failure; and preserved (LVEF>45%) or reduced systolic function (LVEF≤45%). All patients meeting these criteria will be sent an "opt out" letter letting them know that they will be called about the study (letter attached). Each week 25 letters will be mailed to allow ample time for researchers to make calls. The letter will explain the purpose of the study and notify patients that they will be called by a researcher to discuss their potential participation in the study. They will be given the opportunity to "opt out" of this contact by leaving a message on an answering machine. They will be assured that they will not receive a call if they follow this procedure and no personally identifiable information will be retained for patients who opt out. The research assistant will call all patients who do not "opt out." Three calls will be made to attempt to reach each potential participant. Messages will not be left and personal health information will not be shared with family members or others answering the telephone.

We will also work with YCCI to build an EPIC query to identify all patients with heart failure seen in any Yale clinic. This will allow us to identify patients who are not seen in cardiology or sleep clinics. Epic MyChart will be used to identify and notify potential candidates for the study. Patients who have an Epic MyChart account and meet basic inclusion /exclusion criteria will be notified of the study through a MyChart message. The notification will provide an overview of the study. Within MyChart, patients can indicate whether or not they are interested in the study. No patient data will be shared with a research coordinator unless requested by the patient. If a patient selects yes- they are interested in the study, the research coordinator will receive a message requesting that they contact the patient regarding the study. Research coordinators will then contact the patient for eligibility screening. If a patient selects "no," they are not interested in the study, they will not receive any additional messages about the study within Epic, and their information will not be shared with the research coordinator. We will work with JDAT to send recruitment materials to patients who do not use MyChart. JDAT will provide recruitment materials and addresses to the university printing and publishing offices who will coordinate the mailing. Interested patients will call us for further information about the study.

Research Match is a free online recruitment tool that matches studies to volunteers. Yale University is a member institution. We will sign up as a 'researcher,' input relevant details about our study, and Research Match will query its database of individuals who fit certain criteria, in our case, Heart Failure. We will also promote the study by advertising on the Yale Health website's webpage titled "Research Opportunities". Recruitment will also take place at the VA West Haven (see VA IRB approved protocol, attached) using the same process of medical record review and physician referral to identify patients (veterans) with heart failure. These patients will be sent an opt-out letter; the screening and opt-out process described above will be used. The letters will be sent and the phone calls will be made from the VA campus.

A web link to the HIPAA-compliant online survey platform REDCap (https://poa-redcap.med.yale.edu/) will be emailed to heart failure patients who receive care by co-investigator, Dr. Jacoby. These patients and their email address will be identified through JDAT or Dr. Jacoby. These data will be stored in a secure, password protected Yale ITS-managed workstation and only be used to collect survey data about insomnia and to inform patients about the study.

Table 3. Powers to detect the expected effect sizes with a sample size of 100 per group

Outcome Variables	Effect Size	Two weeks post-intervention	Post-intervention measures (3, 6, 12 months)	
		Power	Rho (*)	Power
Insomnia Severity	0.65	99.2%	0.6	99.9%
			0.7	99.9%
			0.8	99.7%
Sleep quality: PSQI	0.46	90.2%	0.6	97.3%
			0.7	95.9%
			0.8	94.2%
Sleep Efficiency (%): PSQI	0.38	76.6%	0.6	89.5%
			0.7	86.3%
			0.8	83.0%
Sleep Efficiency (%): Actigraph	0.70	99.9%	0.6	>99.9%
			0.7	>99.9%
			0.8	>99.9%
Fatigue	0.64	99.5%	0.6	>99.9%
			0.7	99.9%
			0.8	99.8%

We will screen all participants who are not already adherent to positive airway pressure (PAP) for SA with the Apnea Risk Evaluation System (ARES) Unicorder (Watermark Medical, Inc.), a wireless recorder worn on the forehead http://www.watermarkmedical.com/index.php. (Appendix) ARES measures blood oxygen saturation (SpO2) and pulse rate (reflectance pulse oximetry), airflow (nasal cannula/pressure transducer), respiratory effort (pressure transducer - forehead venous pressure), venous volume (photo-plethysmography), snoring (acoustic microphone), head movement, and position (accelerometers). Pulse rate changes indicate arousals. Snoring changes indicate respiratory-related arousals. Forehead venous pressure is a valid measure of respiratory effort.[123] Head position indicates the positionality of obstructive events. ARES distinguishes REM from NREM with EEG, EOG and EMG electrodes at FP1 and FP2 (forehead). The apnea hypopnea index (AHI) is the sum of apneas and hypopneas/hour with 4% oxygen desaturation. Respiratory disturbance index (RDI) is the sum of apneas and hypopneas/hour with 1% desaturation and at least one arousal indicator.

ARES has high sensitivity and specificity[123-125] and better test-test reliability[126] than in-lab PSG. We will record 2 nights and calculate respiratory events/total sleep time because of potential night-night variability and score the data through the manufacturer's website with validated automated methods and review by a board certified sleep technician. Although forehead venous pressure distinguished central vs. obstructive respiratory events,[123] it is not the gold standard, and we will report only the AHI/RDI. ARES minimizes participant burden and cost, compared with PSG. As in our preliminary study, we will give participants the programmed device and instruction, and they will return it personally or by mail. Drs. Redeker and Yaggi will review scored data and provide patients and referring providers with results/recommendations for follow up.

Randomization/blinding. We will use block randomization to assign participants to groups of 6-8 to assure timely filling of groups and group process. CBT can be provided in groups of 3-12, and groups averaging 5 were used for CBT-I.[86] As groups complete baseline, we will randomize to treatment assignment with a computer-generated sequence. Recruitment/screening/data collection/data entry personnel will be blinded to group assignment. It is impossible to blind participants, but they will not know the group assignment until the first meeting. Interventionists will be blinded to baseline data and specific hypotheses.

Treatment: CBT-I ("Healthy Sleep" Group: HS). Our manualized protocol includes CBT-I elements (Table 1) in 4 bi-weekly one-hour sessions;[127,128] a call on alternate weeks; the HS Guide, a workbook with CBT-I components, with sixth grade reading level, print appropriate for older adults, and images reflecting diversity (Appendix); and optional hypnotic tapering. About 80% of hypnotic users selected tapering in our pilot, and we expect hypnotic use to decrease, based on the literature[81,82] and our experience.[20] Four bi-weekly sessions of CBT-I were superior to other frequencies.[129] The group format was feasible in our pilot, and will enhance social support and learning. Use of a CBT-I trained APRN interventionist is consistent with our[29] and other[94] studies and will promote sustainability due to the greater availability of APRNs than sleep psychologists.

The advanced practice nurse (APRN) interventionist will briefly review the HH Guide (HF self-management). Homework includes CBT-I skills practice and daily tracking of CBT-I use, sleep, symptoms, and weights in a HS Log. We will provide an electronic scale, the HS/HH Guides, instructions, schedules, progressive muscle relaxation recordings, videos of sessions, and HS logs programmed with Qualtrics ™ software on a mini-tablet computer that participants may keep. Logs will be time stamped and uploaded from the tablet to the Yale server when WI-FI is available, but WI-FI is not necessary for data entry or the time stamp. Therefore,

participants do not need WI-FI in their homes. We piloted this method and found it feasible. Completion of the logs takes < 10 min/day. However, to accommodate participant preferences[88,130] and to promote adherence[131] we will provide both paper and electronic options that produce equivalent results when training and reminders are provided,[130,131] in contrast to "batch effects" when paper diaries are used without reminders or training.[132,133] We will text message or phone participants every other day to remind them. Group differences in paper/electronic use are unlikely due to randomization, careful training, reminders, and equal study team contacts, but we will explore the possible effects of unbalanced usage. Web applications are available for CBT-I,[134-136] but we will not use them because of the need for consistent interactions/social support between groups.

Most CBT-I studies used usual care, wait-list, or information-only controls, but we will use attention-control because time and attention may improve symptoms and function. The **Attention Control ("Healthy Hearts:" HH)** includes didactic sessions with HF self-management education[46,137] (Table 1), supported with the HH Guide (Appendix), developed from the "Fight against Heart Failure Workbook.[137] Sessions, homework, and the HH Guide are equivalent to CBT-I in frequency, duration, and interventionist time. Sleep hygiene is included, but not the active ingredient[24,80,138] and was the control in past trials.[93,139] There is information on relaxation/stress, but no relaxation homework. We will explain that HF self-management may improve sleep by improving HF management. Homework includes practice of HF self-management and tracking these skills, symptoms, and daily weights in a HH Log. We will provide all materials, including HH session videos, HH Guide, HH Logs (except the relaxation script and CBT-I video) formatted identically to those for the HS group.

We will hold group sessions in the Biobehavioral Research Laboratory at Yale School of Nursing where there is ample parking, shuttles to/from clinical sites, video conferencing, and recording capability. We will provide rest periods and healthy refreshments and review HH/HS logs at each session to guide practice. We will use scripted telephone boosters of ~10 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. We had no difficulty with these methods that were highly acceptable in our preliminary study.[28]

As in our pilot, we will send birthday/holiday cards to maintain contact and promote retention. We will provide $50 for ARES screening and $250 disbursed over data collection/treatment for travel/time and taxi fare if needed. To promote retention and adherence after intervention, we will use brief scripted monthly phone calls until the12 month F/U, with content identical to the earlier calls, except meeting reminders. Some attrition is unavoidable, but our strategies will minimize it. We will resume data collection at later milestones if participants miss data points and track reasons for missing data and/or attrition.

We will run group series simultaneously to offer options for time of day/day of week and offer makeup sessions with another ongoing group, but telephone or Skype make-ups will be used for those unable to attend in person due to weather or other reasons. 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. Tele-health CBT-I was successful in non-HF patients,[136] and phone-delivered CBT is efficacious in cardiopulmonary[140] and mental health disorders.[141,142] We will compare groups on the phone/Skype vs. face-face sessions and attendance and include the number and types of sessions in analyses if groups are unbalanced.

The study is designed to assure treatment fidelity (consistent dose, frequency, and contacts), and we will use similar materials/homework in both manualized conditions (Appendix). We will use protocols we developed to train study personnel. Separate interventionists, blinded to baseline/outcomes data and study hypotheses, will provide both treatment conditions to avoid contamination, and single interventionists will provide each condition. To assure protocol adherence, we will record sessions and script and record phone calls. With published methods,[143] 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.

Data collection. We will conduct medical record review and interviews for clinical and demographic data. Participants will complete questionnaires and 2 weeks of continuous wrist actigraphy/diaries at home and a Six Minute Walk Test (6MW) and Psychomotor Vigilance Test (PVT) with standard methods at the YSN Biobehavioral Research Laboratory at the end of the 2-week monitoring. These measures will be obtained at baseline (B/L) and each follow-up (F/U) (2 wks, 6, , 12 months). We will obtain actigraphy/diaries for 2 weeks as recommended due to high variability in sleep characteristics (e.g., sleep latency, efficiency) in insomnia,[144] consistent with many past CBT-I trials (e.g.,[95]). Sleep diaries (as the logs) will be offered in paper and electronic format and used to assist in interpreting the actigraph data (reasons for removal, lights "out/on" times), but not to generate outcomes. Participants had no difficulty with 2 weeks of diaries/actigraphy in our

pilot and found procedures acceptable, so burden is not a concern. As in our pilot, we will deliver materials by overnight mail or home visit, phone participants within a day of receipt; and review instructions (remove actigraphs only for bathing, depress event markers at "lights out/on" and removal times). Time for form completion, 6MW and PVT are ~1 hour/collection period and actigraphy/diary time: < 10 minutes/day. To elicit event free survival (EFS), we will interview participants and conduct medical record review during scheduled contacts for 12 months and call every 2 months thereafter through the first half of study year 5.

Independent and dependent study variables/measures. We will use self-report and objective measures of insomnia/sleep (Table 4). The Insomnia Severity Index (ISI), based on ICSD-2 criteria,[106] is internally consistent (0.74 – 0.88)[104,145] and sensitive to treatment.[104,145,146] The Pittsburgh Sleep Quality Index (PSQI),[147] a legacy measure,[51] has diagnostic sensitivity (89.6%) and specificity (86.5%) for distinguishing "good" vs. "poor" sleepers[147] (Alpha = 0.83 in HF)[8] and will be used to calculate self-reported sleep duration, sleep efficiency (SE) [(total sleep duration/time in bed) X 100], latency, and global sleep quality. To allow comparison with PROMIS studies, we will administer the PROMIS sleep quality brief item bank, a validated and precise measure.[51] We will use the Respironics Minimitter Actiwatch AW2, a wrist-worn actigraph, to elicit objective sleep variables. Correlations between actigraphy and polysomnography (PSG) range from 0.82-0.98 (SE) and 0.90-0.97 (duration) in normal sleepers;[148-154] correspondence is good in insomnia.[155] Actigraphs are sensitive to treatment[156] and cardiac patients were adherent.[19,157] Actigraph-recorded sleep latency is not always stable, but is associated with NY Heart class (unpublished). We will use the AW2, rather than a publicly marketed accelerometer, because it is valid and reliable. Per recommendations,[158] participants will complete a daily diary based on the Consensus sleep diary[159] to identify lights out/on, times/purpose of removal, and hypnotic use. The diary will be provided in the same format as the logs (See treatment). PSG is not diagnostic for insomnia and increases burden and cost.
Symptoms will include fatigue, sleepiness, sleep-related impairment, pain, anxiety, dyspnea, and depression because these are common in insomnia and HF (Table 4); cluster together and were associated with insomnia remission in our pilot. The Multi-Dimensional Assessment of Fatigue Scale (MAFS)[160] has concurrent (r = 0.84) and divergent (r = -0.62) validity and internal consistency (alpha= 0.84 in HF).[10] The Multi-Dimensional Assessment of Dyspnea Scale (MADS), adapted from the MAFS, is reliable (alpha = 0.94) and valid.[10] The Epworth Sleepiness Scale (ESS)[161-163] is reliable and valid[162,163] (alpha = 0.87 in HF).[10] The PROMIS Sleep-Related Impairment brief item bank,[51] a valid and precise measure, will enable comparison with emerging studies. We will measure Psychomotor Vigilance (PVT)[49] with the PVT-192 (Ambulatory Monitoring, Inc. Ardsley NY) with the 10 minute protocol,[50] detecting lapses/reaction time. PVT is valid when administered as a single measure in the clinic setting,[50] used in HF patients,[3] and associated with fatigue and quality of life.[164,165] The PROMIS™ 8-item short-form elicits fatigue and anxious and depressive symptoms. The PROMIS™ Pain intensity and Pain Interference item banks will be used to measure pain. The PROMIS™ measures are based on item-response theory and are responsive to clinical change.

We will measure functional performance with the Medical Outcomes Study (MOS) SF36v2 Physical Function Component[175] (reliable and valid in HF);[175-177] and the Six Minute Walk Test (6MW)[178] (correlated with oxygen consumption,[179] cycle ergometry, HF prognoses, and self-reported function)[178] with standard methods.[180] With the exception of PROMIS, BPI, MW and PVT, the measures were used in our preliminary work and participants did not view them as burdensome. We have experience with the 6 MW[53,181] and PVT.[181]

We will conduct cost-effectiveness analysis (CEA) from a societal perspective where all costs are considered, regardless of who incurs them,[182,183] document resource use in units, and apply prices to units. Data will be obtained by self-report and validated through the EMR, hospital cost accounting database, and the Medicare fee schedule. Variables will include direct costs for health care resources used [office and emergency department visits, homecare, hospitalizations (and reasons, e.g., HF), cardiac devices, over the counter (OTC) and prescribed medications]. A sub-set of our team, blinded to group assignment, will review hospitalization/ED/office visits and evaluate causes. We will use the electronic pharmacy system to obtain prescription drug utilization and self-report for OTC medications. We will determine costs for prescription and OTC medications with Redbook average wholesale prices and public market prices from drugstore.com. We will include payments to the interventionists and costs of intervention materials. Deaths and causes of death will be ascertained with the EMR. If not found, we will query the National Death Index. Indirect costs will include self-reported time missed from work, travel, and self-management and CBT-I activities. We will measure effectiveness as quality adjusted life years (QALY), estimated from the EQ-6D algorithm from SF-36 data[184] and track research-related costs (monitoring, data collection, personnel costs, and subject payments).

Table 4. Primary Study Variables and Measures: *Baseline, 3 months, 6, 12 months*

Variable	Measure
Sleep/Insomnia	
Global Sleep Quality	Pittsburgh Sleep Quality Index (PSQI); PROMIS Sleep Disturbance Brief Item Bank
Sleep latency (SL), wake after sleep onset (WASO), efficiency (SE), time in bed (TIB), total sleep time (TST)	Subjective: PSQI Objective: Actiwatch2/Wrist Actigraph
Insomnia Severity	Insomnia Severity Index (ISI)
Symptoms	
Excessive Daytime Sleepiness	Epworth Sleepiness Scale (ESS); PROMIS Sleep Impairment Brief Item Bank
Fatigue (total, severity, distress, interference, timing)	Multi-dim Assessment of Fatigue Scale (MAFS)
Depressive Symptoms	PROMIS Depression Short Form 8a
Anxious Symptoms	PROMIS Anxiety Short Form 8a
Pain (severity, location, and interference)	PROMIS Pain intensity-3 item; PROMIS Pain Interference
Dyspnea (total, severity, distress, interference, timing)	Multi-dim Assessment of Dyspnea Scale (MADS)
Neurobiological effects of sleep loss/sleepiness	Psychomotor Vigilance Test (PVT-192)
Functional Performance	Self-report: SF36 v2 Physical Function Component; Objective: Six Minute Walk Test (6 MW)
Health Care Resource Utilization	Direct and Indirect Costs (See narrative)
Event free survival	Absence of: death (all cause), HF hospitalizations; HF ED visits; heart transplantation, LVAD EFS = time to first event

Event-free survival (EFS) will include time without events listed in table 4 and will be tracked through the second quarter of study year 5, 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 electronic medical record (EMR); a sub-set of our team blinded to group assignment will review data to determine cause of death/hospitalization. We will query the National Death Index if information is otherwise unavailable.

Clinical and demographic variables. We will use interview and EMR to track demographic/clinical data: sleep and medical history, comorbidity (e.g., osteoarthritis); prescribed and over-the-counter (OTC) medications (especially ACEI/ARBs and beta blockers that improve survival and prescribed/OTC hypnotics); SA; PAP use; LVEF; NY Heart class; cardiac devices; and HF stage. Self-report data will be validated through EMR and vice-versa. The Charlson Comorbidity Index[185] and Seattle HF Risk Model, a predictor of death,[186] will be computed. Due to the possible influence of self-care/self-management, including adherence to HF disease management, we will use the 8-item Morisky Scale,[187] a reliable and valid measure of medication adherence, and the reliable and valid self-care maintenance and management scales of the Self Care in Heart Failure Index (SCHFI v.6)[188,189] These variables will be measured at baseline and all f/u periods.

Satisfaction/acceptability. As in our pilot, we will elicit satisfaction/acceptability with the treatment and control, materials, and logistics with an adapted version of the Treatment Evaluation Questionnaire (TEQ).[129,190] We will use a 0-10 (10 = high) rating scale for each item (e.g., treatment helpfulness; willingness to continue; degree of "cure;" satisfaction with scheduling, provider, delivery methods, and take home materials, including electronic or paper format). This evaluation will occur after the 8 week treatment.

We will evaluate treatment enactment/adherence (CBT-I and HF self-management skills use) with bi-weekly calls and review of the HH and HS logs (See treatment section). We will use the Morisky Scale and SCHFI V.6. to assess self-care/self-management (see variables/measures) and evaluate participant flow with CONSORT,[191] attendance, and reasons for non-participation, and attrition.

Data Management and Statistical Analysis Plan. We will use REDCap, an NIH-supported electronic data capture application[192] to develop data collection forms. The Yale Program on Aging (POA) hosts Yale's implementation of REDCap (See resources). Data will be entered directly into REDCap with tablets, but we will provide printed forms for all instruments if tablets are not available or fail. Blinded staff will not have access to intervention forms or data. REDCap and study-specific tools and data will be the basis of an administrative system that will support field operations. This blinded tool will enable tracking of recruitment, retention and study progress, scheduling and managing telephone calls, and managing/reporting adverse events. We will develop a separate unblinded database tool for managing intervention schedules and adherence. We will maintain a read-only, de-identified SAS data mart that will be updated daily and will be the basis for conduct-of-study, error-check, and data safety/monitoring reports. Snapshots of the data mart will be used for interim and final analyses.

Data Analysis. We will use Actiware v.6 software (Respironics Minimitter, Inc.) to score actigraph data. Personnel blinded to group assignment will use event markers, light meter and diary recordings to identify "lights on/out" and removal times and to summarize actigraph variables over the 2-week intervals. Use of three methods will minimize problems with missing data (e.g., occlusion of the light meter) for single indicators. Wrist-worn light meters are valid measures of ambient light.[193]

To identify outliers and data errors, we will use logical data checks and handle missing data with the assumption of missing at random (MAR), an approach that assumes missing values have the same patterns as complete data. We will impute missing data on survey items with Rubin's[194] multiple imputation method, replacing missing values with simulated sets of imputed values from Monte Carlo simulation, and analyze each simulated completed dataset with standard methods. Results will include estimates and confidence intervals that incorporate the uncertainty of imputed values. Generalized Linear mixed Models (GLM) and General Estimating Equations (GEE) allow the use of incomplete repeated measures due to dropout, If there is at least one baseline and follow-up data point. This approach will minimize the effects of sample loss due to attrition

We will compute univariate statistics to examine frequency distributions of categorical variables and normal distributions for continuous variables with box plots and the Shapiro Wilkes test to assess normality. We will test differences in demographic and clinical variables (e.g., SA, LVEF), and baseline adherence, self-care, and self-management (see inclusion/exclusion criteria; clinical/demographic variables) between the two randomized groups to determine the success of randomization. Because some clinical and demographic variables, including PAP use, may influence outcomes, we will include them as covariates in multivariate models if groups are unbalanced on these variables at baseline.

We will use descriptive statistics to describe clinical and demographic characteristics by treatment group and time. To evaluate differences in insomnia severity, sleep characteristics (Aim 1a), symptoms, PVT (Aim 1b) and functional performance (Aim 2) over the four time points (baseline, 3, 6, and 12 months), we will use GLMM with a repeated measures statement to examine group, time, and group by time effects. Nonlinear time effect will be controlled by transforming a continuous time variable with cube root form, which allows to estimate relatively rapid change in early at post-intervention than the follow-ups. We will choose the best covariance structure (compound symmetry vs. unstructured vs. moving average) by comparing the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). In multivariate models, adjusted intervention effects will be estimated by including covariates that might differ by group assignment (e.g., LVEF, comorbidity, age, SA with CPAP use). We will assess multi-collinearity among covariates with the variance inflation factor (VIF) and eliminate variables with high VIF (> 10) if the intervention effect is not modified after elimination. We will identify influential outliers with DFFITS, DFBETAS, and Cook's distance. If there are non-normally distributed residuals, the outcome variable will be transformed to ordinal form or fitted with more flexible distributions (e.g., Gamma, Poisson). We will use GEE with a robust working correlation structure to address within-subjects correlations for changes in outcomes with clinical cutoffs (i.e., ISI≥, ESS≥10, PSQI≥5, SMW≥1000) over time. To avoid the inflation of type 1 error, False Discovery Rate (FDR) will be calculated for post-intervention effects on 13 outcome variables.

For cluster analysis (Aim 1c), we will use Latent Transition Analysis (LTA)[195,196] to produce a latent variable categorizing a symptom cluster at baseline and follow-ups. Consistent with methods in cardiac samples[166] each participant will be stratified into a symptom cluster group, based on dichotomized symptom severity. In our pilot, we found 3 clusters (I: mild); (II: high pain/dyspnea); (III: severe – high depression. anxiety, sleepiness). We expect LTA to produce two or more clusters of 2 or more symptoms characterized by symptom severity and patterns of correlated symptoms. LTA provides the item-response probability of having a specific symptom in each symptom profile group and the probabilities of membership in each symptom profile at each time and transitioning from one symptom profile to another. SEM and other similar latent variable methods do not quantify symptom cluster membership and transitions between clusters over time. The LTA model will include a group variable as a covariate to test the effects of CBT-I on membership in a symptom cluster and transition between clusters over time.

We will use GLMM or GEE to determine the extent to which the effects of CBT-I on insomnia, sleep characteristics, symptoms and functional performance at 6 and 12 months are non-inferior to outcomes at two weeks. (Aims 1a, 1b, 2). We will identify potential barriers to sustained intervention effects (e.g., LVEF, comorbidity, PAP treated SA, self-care/self-management) by testing interactions between time and covariates associated with outcomes.

To address Aim 3, we will perform stochastic cost-effectiveness analysis (CEA) from the perspective of society. We will document resource utilization in units for direct and indirect costs (above) 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 CEA

is to estimate the incremental cost per additional unit of effectiveness, measured as QALYs, the standard in cost-effectiveness research and economic evaluations of sleep disorders.[101] We will estimate QALYs by applying the utility measure derived from the 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 summarize the cost-effectiveness of CBT-I relative to HH with an incremental cost-effectiveness ratio (ICER):

$$\text{ICER} = \frac{C_{CBT-I} - C_{HH}}{E_{CBT-I} - E_{HH}}$$

(C_{CBT-I}: expected cost of the intervention; C_{HH}: expected costs for the HH group; $E_{CBT-I:}$ effectiveness of the intervention, measured as QALYs;E_{HH}: effectiveness in the HH group). ICER represents the incremental cost to gain an additional QALY with CBT-I. We will discount costs over the 3 years of data collection and estimate uncertainty around the ICER by bootstrapping, yielding a 95% confidence ellipse around the ICER. In the usual cost-effectiveness framework, a willingness to pay threshold is used to determine cost-effectiveness of a treatment. However, in a stochastic cost-effectiveness framework, we can estimate the probability that CBT-I is cost-effective over a wide range of willingness to pay thresholds with the cost-effectiveness acceptability curve (CEAC). We will perform sensitivity analyses for costs, life expectancy, and utility.

We will use survival analysis for exploratory aim 1 and compare time to EFS between CBT-I and the attention control condition with a competing risk approach.[197] This approach accounts for the relationship of the occurrence of one event with others. Participants who do not experience events during f/u will be right-censored. As a secondary analysis, we will examine time to specific events (e.g., hospitalization, death). We will adjust the survival model by including baseline Seattle Heart Failure score,[186] depression, LVEF, adherence,[36] and self-care/self-care management,[77] as they predicted EFS.

Table 5. Timeline for study activities

	Quarters of Years 1-5																			
Activity	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Hire & train personnel	X	X																		
Prepare study materials	X	X																		
Recruit & screen		X	X	X	X	X	X	X	X	X	X									
Provide treatment			X	X	X	X	X	X	X	X	X	X								
Collect data		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Analyze data				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Present/Publish									X	X	X	X	X	X	X	X	X	X	X	X

Challenges/rationale. Although desirable to include non-English speaking patients, translation is beyond available resources. Inclusion of patients with mild SA is safe and will yield a sufficient sample. We successfully included PAP-adherent SA patients in our pilot, with an equivalent proportion in each group. Attrition was low, but we expect more in a longer study due to HF exacerbation and other events. We will over-recruit and use retention and intent-to-treat strategies. If a patient misses a follow-up, we will follow at the next time point if possible. We will include patients who are stable at B/L and have evidence-based HF disease management because uncompensated HF and/or poor disease management may confound outcomes. Randomization will promote group equivalence, and we will explore possible confounding effects of clinical and demographic factors on the outcome variables. Participants had no difficult completing the intervention and measures in our pilot and very few participants may be unable to complete the 6MW. Duration of EFS tracking will vary (18-45 months) based on enrollment time but is unavoidable due to total study duration. The five-year study will provide sufficient time to obtain meaningful results. It is possible that HF self-management education may improve health care resource utilization and EFS, but our pilot suggests that CBT-I had a larger effect, and a previous study[78] showed no effect of HF self-management on this outcome. Comparison of group effects on this outcome is an important goal of the study. Because of the plan for extended follow-up, we will not offer cross-over from the attention-control into the CBT-I condition, and we will track changes in insomnia and self-management behavior over time. The results will be generalizable to HF patients who have chronic comorbid insomnia – approximately half of HF patients.[8] Future studies will address effectiveness, dissemination and translation of CBT-I into diverse HF settings.

PROTECTION OF HUMAN SUBJECTS

Risks to Human Subjects

a. Human Subjects Involvement and Characteristics

1. Involvement of human subjects

Recruitment & screening:
Health care providers will identify potential candidates for the study and elicit their consent to be contacted by a member of the study team, or potential participants could respond to advertisements to the study and contact the study team. A member of the study team will contact participants. Screening for participation will include medical record review and patient interview to determine whether participants meet the enrollment criteria (see characteristics of the study population). We will also use the PHQ-9 depression scale, a component of the PRIME-MD, to screen for depression. Those who score in the moderate-severe range (score of 15 or higher) will be further evaluated for depression using the Structured Clinical Interview for Depression. Those who have a suicidal ideation or have severe depression or bipolar disorder will not be included in the study. All others will be invited to participate in the study, because several studies have shown that CBT-I improves mild and moderate depression. Medical records will be reviewed with patient consent to elicit health and medical history, and medications. (See characteristics of study population). Participants will be consented for further screening and study participation. All participants who are not already in treatment for sleep disordered breathing will be screened in their homes with a portable sleep recorder (ARES), after detailed instruction. Participants with an apnea hypopnea index < 10 or who have sleep apnea and are adherent to positive airway pressure for $\geq$ 6 hours/night will be included in the next phase of data collection.

Data collection: Participants who meet the study criteria and agree to participate will complete a battery of questionnaires to elicit self-reported symptoms, functional performance, and characteristics of sleep. They will also complete forms to indicate their use of heart failure self-management and self-care behaviors. Participants will wear wrist actigraphs (accelerometer device that is approximately the size of a sports watch) for 2 continuous weeks, removing them only for bathing. They will be reminded not to cover the actigraph with clothing or bedclothes because this will obscure the light measurements. Participants will simultaneously complete a diary to note characteristics of sleep, use of hypnotic medications, and times of lights out and lights on related to sleep time, as well as removal (and reasons) of the actigraph. These data will be used to assist in scoring the actigraphy data, and participants will have the option to complete the diary on paper or on an electronic device. At the end of this screening period, participants will visit the Yale School of Nursing Biobehavioral Laboratory where they will complete a six-minute walk test and a psychomotor vigilance test.

The questionnaires, diaries, actigraphy, six minute walk, and psychomotor vigilance test will be repeated at baseline, 3 months (2 weeks after participating in the treatment/control conditions), and at 6 and 12 months.

In addition to the primary study variables noted above, medical records will be reviewed and participants will be interviewed over each of the study time periods to elicit changes in health status, medication use, any additional treatments, and use of health care resources (e.g., visits to health care providers, hospitalizations, emergency department visits, medications, as well as time off from work, time associated with use of the CBT-I and self-management skills practice, and other possible costs associated with the intervention and heart failure. These data will be obtained through the 12-month follow-up period.

After the 12-month follow-up, a member of the study team will contact participants every 2 months until the end of the 5 year study period to obtain information on health status, hospitalization/emergency department visits (and their causes), possible heart transplants, or implantation of a left ventricular assist device in order to measure events used to calculate event free survival. This may result in between 18 and 45 months of follow-up depending on when participants are recruited into the study.

Intervention phase:
Participants will be randomized in groups of 6-8 into the intervention group (cognitive behavioral therapy for insomnia – CBT-I: “Healthy Sleep Group:”HH) or into a comparison group condition that will include information on self-management of heart failure and sleep hygiene information (“Healthy Hearts Group:” HH). Participants will not know the group to which they have been randomized until they arrive at the meeting. Participants in both groups will attend 4 bi-weekly face-face one-hour sessions and participate in 4 15-minute telephone calls (each of the 4 weeks alternating with the face-face sessions). The calls will consist of 1) reminders to continue using the strategies taught in the sessions 2) clarification of questions or problems with the prescribed activities (attention or control); 3) reminders/clarification regarding completion of the logs, and 4) reminders about the time and place for the next session. If unable to attend isolated group meetings, they will participate by telephone conference call or Skype. They will also be able to make up single sessions by telephone or Skype.

The CBT-I group will receive instruction on techniques to improve their sleep and be expected to practice these techniques at home. These techniques will be included over the 4 face-face meetings in which the therapist will teach and provide examples and feedback on individual progress with each of the activities. There will be an opportunity for questions and discussion. The therapist will provide feedback at each session. CBT-I includes stimulus control; sleep restriction, cognitive therapy, relaxation, and optional tapering of hypnotic medications. They will participate in a brief discussion covering HF medications, symptoms, management of fluids and when to call their health care provider about HF symptoms.

Stimulus control utilizes instructions designed to re-associate the bed/bedroom with sleep and to re-establish a consistent sleep-wake schedule. Patients are instructed to: go to bed only when sleepy; get out of bed when unable to sleep; use the bed only for sleeping; arise at the same time each morning; and avoid napping.

Sleep restriction is designed to limit the actual sleep time to improve sleep efficiency. Under the supervision of the therapist, the patient decreases time in bed to maximize the percentage of time asleep. Time in bed is gradually increased based on sleep efficiency, until the optimum sleep duration/efficiency are obtained.

Cognitive therapy addresses misperceptions about insomnia, clarifies misattributions of consequences of sleep, clarifies and reframes unrealistic expectations about sleep, reduces performance anxiety, increases control, and clarifies faulty beliefs about sleep. The therapist will work with participants to adopt 6 basic strategies: (1) “keep realistic expectations; (2) do not blame insomnia for all impairments; (3) never try to sleep; (4) do not give too much importance to sleep; (5) do not catastrophize after a poor night’s sleep; and (6) develop tolerance for the effects of insomnia.[26, p. 37]

Relaxation therapy is focused on reducing somatic and cognitive arousal. We will use progressive muscle relaxation to reduce somatic arousal, combined with a cognitive focus on diaphragmatic breathing through a scripted relaxation protocol. Participants will be provided a recording of the scripted relaxation exercise on a min-tablet computer or an MP3 player if they prefer.

Sleep hygiene education focuses on managing external factors that may affect sleep. Although there is variation between studies on elements used,[198] the core elements are avoidance of caffeine, tobacco, and alcohol during the evening hours, modification of the sleeping environment (comfortable bed, temperature, noise, lighting),and avoidance of exercise near bedtime. Sleep hygiene often includes information about normal sleep and age-associated changes.[24] We will include this and information about the potential interactions between HF, its treatment and sleep/insomnia

Hypnotic tapering is an option for the CBT-I group. This includes gradual reduction in use over the counter or prescribed hypnotics guided by the therapist. Participants may choose or not choose this option.

Participants will be expected to practice the HS behavior at home and record them, their daily weights, sleep and symptoms in a Health Sleep Log that will be available in paper or electronic format. They will receive an electronic bathroom scale and videos of the CBT-I session, the recorded relaxation exercise, the HS Log, instructions for all study elements, and study schedules on a mini-tablet computer. If they prefer, these materials can be used on an electronic device (smart phone, tablet, computer) of their choice. If they prefer, paper copies of all materials will be made available. In addition to the Healthy Sleep Guide, the CBT-I group will receive the Healthy Hearts Guide, a workbook that includes strategies for self-management of heart failure (See below). They will be encouraged to use the tablet for recording into the logs. The information will be uploaded to the Yale server when WIFI is available but can also be completed offline.

The participants who are randomized to the heart failure self-management group (“Healthy Hearts”) will receive 4 bi-weekly one hour sessions of classes on aspects of managing heart failure, including information about the disease process, symptoms, medications, exercise, managing weight, fluid, and diet, and basic information on stress management and sleep hygiene. Improvement of disease management, including sleep hygiene, physical activity, use of medications, avoidance of sodium etc. may improve sleep. Therefore, patients will be informed that this may be the case. They will be encouraged to use the techniques learned while at home. Participants in the “Healthy Hearts” group will receive the Healthy Hearts Guide, based on the “Fight against Heart Failure Handbook” with information on aspects of HF disease management, and a digital scale for monitoring of daily weights. The duration and scheduling of the HH group will be identical to the HS group. Participants will complete HH Logs to track their daily weights, and use of the self-management strategies and symptoms. Like the Healthy Sleep Group, the participants will receive information materials on a mini-tablet computer or in paper format. They will receive the Healthy Hearts Guide, a video of the HH intervention

sessions, the HH logs, instructions for all elements of the study, and schedules. They will not receive the CBT-I video, HS Logs, HS Guide or the relaxation script.

Follow-up data collection

Data collection will proceed during the follow-up periods as noted above. Participants will be called monthly after the intervention phase until the 12-month follow-up. These calls will elicit any changes in health status and medications, health care utilization (hospitalization, provider visits, emergency department visits, home care use, changes in work status, time associated with the self-management/CBT-I activities). The caller will also elicit concerns about the HH or HS skills, provide problem solving, and remind participants about the next follow-up period. After the 12-month measurement period, participants or their designated family member will be called bi-monthly to elicit changes in health status (hospitalizations, heart transplant, implantation of cardiac devices or artificial hearts, or death) until the end of the study duration. Participants will be informed of the potential duration of follow-up, based on when they were recruited into the study (18-45 months).

Participant will receive $50 for the sleep apnea screening; and an additional $250 disbursed over the study milestones. They be able to keep the mini-tablet (estimated value $60), and the study will provide taxi fare if needed.

2. Characteristics of the study population

The sample will include 200 individuals ≥ 18 years of age with NY Heart Class II-III HF who are cognitively intact by clinical impression, speak/read English, concerned about their sleep for ≥ month, and score ≥ 8 on the Insomnia Severity Index,[104] an indicator of ICSD-2 insomnia.[106] Participants will have preserved (LVEF > 45%) or reduced ejection fraction (LVEF ≤ 45%). LVEF was not associated with chronic insomnia,[8] but may contribute. HF patients at the recruitment sites undergo annual echocardiography and with cardiac changes. We will use the most current LVEF. Although sleep continuity is negatively related to age, we will include adults of all ages because of the greater effects of insomnia on fatigue in younger adults.[8] Participants will receive HF care per the AHA/ACCF guidelines,[35] as provided in the study recruitment sites.

Depressive symptoms are common in HF[10] and often comorbid with insomnia. CBT-I improves depression,[98,107,108] including suicidal ideation,[109] and antidepressants[94] and depression[199] did not diminish its effects. We will include patients with no/moderate depression and those on anti-depressant, anxiolytic and/or hypnotic medications because hypnotic tapering is an effective part of CBT-I.[81,82]

Exclusion criteria are untreated restless legs syndrome; night/rotating shift work; travel across 2 or more time zones within one month of enrollment; contraindications to sleep restriction [seizure disorder, severe sleepiness (Epworth Scale >18), bipolar disorder]; neurological/musculoskeletal conditions affecting the non-dominant arm (use of wrist actigraph), active illicit drug use, dementia, and end-stage renal failure. Participants who are hospitalized or have emergency department visits, unstable conditions, or changes in vasoactive medications within 4 weeks of recruitment will not be enrolled until 4 weeks elapse without new events. Patients with these events after enrollment will be retained; events will be tracked and included in analyses.

Chronic insomnia and sleep apnea (SA) are often comorbid with HF,[110-112] but SA was not associated with insomnia in HF patients[3,8] and did not affect CBT-I outcomes in older adults.[94] Although positive pressure (PAP) improves some cardiac variables, lack of rigorous long term RCTs preclude widespread SA treatment in HF,[113] and the lower treatment threshold is not well defined.[113-115] Most studies were small, poorly controlled, and included patients with moderate-severe SA (apnea hypopnea index/AHI ≥ 15).[115] One study (n = 40 completed)[116] had participants with AHI > 5, but mean AHI was ~ 28, and the authors did not report the proportion with mild SA. Given limited evidence of PAP benefits in very mild SA, we will include patients with AHI < 10 and refer those with AHI ≥ 10 for further evaluation in collaboration with Dr. Yaggi. Participants with significant SA will be eligible If adherent to PAP ≥ 6 hours nightly for at least 3 months. Titration of PAP or conduct of home sleep studies during PAP treatment is beyond the scope of this study, but participants will be eligible if they continue to have insomnia once adherent to PAP.

Vulnerable groups

No fetuses, neonates, pregnant women, prisoners, institutionalized individuals, or others who may be considered vulnerable populations will be included. In the state of CT, individuals 18 years of age and older are considered to be adults and are able to provide written informed consent.

3. Recruitment
Participants will be recruited through the Yale New Haven Hospital (YNHH) Heart Failure and Transplantation Center, and the VA Connecticut health Care System. We will also have access to the Yale Primary Care Center, a community based primary care program and the Yale Sleep Medicine Clinic. These sites use the AHA/ACC guidelines for management of HF. Potential participants will be identified by health care providers in these settings. Providers will elicit permission for the study team to contact the participants, and a member of the team will approach the patient, explain the study, and obtain informed consent for initial screening. We will also screen medical charts and sent invitation letters by mail. Epic MyChart will also be used to identify and notify potential candidates for the study. Patients who have an Epic MyChart account and meet basic inclusion /exclusion criteria will be notified of the study through a MyChart message. The online recruitment tool "Research Match" will be used to advertise the study, along with Yale websites.

b. <u>Sources of Materials</u>
1. Research material
The sources of materials will include medical records (including electronic medical records), the hospital cost-accounting database, patient self-report and recordings of sleep, Psychomotor vigilance, and six-minute walk test performance.

2. Description of data to be collected
Data collection will include self-reported and actigraph-recorded characteristics of sleep, insomnia, fatigue, depressive symptoms, anxious symptoms, excessive daytime sleepiness, pain, dyspnea, and sleep-related impairment. Functional performance (ability to complete daily roles and activities) will be assessed by self-report and through a 6 minute walk test (a test of the distance walked in 6 minutes). Measures of physiological data, including oxygenation, respiratory effort, and airflow will be obtained in a screening evaluation for sleep apnea. Participants will also complete a psychomotor vigilance test to evaluate reaction time and vigilance associated with sleep loss. We will obtain information on participants' perceptions about their satisfaction with treatment and acceptability of the study activities. We will review medical and administrative records, as well as death certificates if necessary to determine health care utilization and survival.

3. Access to private information provided by the participants
Only members of the study team will have access to private information collected from the study participants.

4. Collection of the information specifically for this study
Data collection will include self-reported and actigraph-recorded characteristics of sleep, insomnia, fatigue, depressive symptoms, anxious symptoms, excessive daytime sleepiness, pain, dyspnea, and sleep-related impairment. Functional performance (ability to complete daily roles and activities) will be assessed by self-report and through a 6 minute walk test (a test of the distance walked in 6 minutes). Measures of physiological data, including oxygenation, respiratory effort, and airflow will be obtained in a screening evaluation for sleep apnea. Participants will also complete a psychomotor vigilance test to evaluate reaction time and vigilance associated with sleep loss. We will obtain information on participants' perceptions about their satisfaction with treatment and acceptability of the study activities. We will review medical and administrative records, as well as death certificates if necessary to determine health care utilization and survival. The initial interview will take approximately ½ hour, completion of the actigraphy and diaries will take approximately 10 minutes each day during the 5 data collection periods. The actigraphy will be completed over a 2-week period of time at each time point. The questionnaires will take no more than an hour at each of the 5 time points.

We will screen for SDB with the Apnea Risk Evaluation System (**ARES) Unicorder** (Advanced Brain Monitoring, Carlsbad, CA), a wireless physiological recorder worn on the forehead and measures blood oxygen saturation (SpO2) and pulse rate (reflectance pulse oximetry), airflow (nasal cannula/ pressure transducer), respiratory effort (pressure transducer sensing forehead venous pressure) and venous volume (photoplethysmography), snoring levels (calibrated acoustic microphone), head movement and position (accelerometers). It is small and comfortably worn in all sleep positions, and is easily applied by the user with simple instruction. Participants will wear the recorder for 2 consecutive nights.

Participants will wear the actigraph continuously for 2 weeks, removing it only for bathing, depress the event marker at "lights out" and "lights on" times to demarcate time in bed, and keep the light meter on the actigraph uncovered. Instructions will be provided. Sleep diaries will be completed daily to assess time of lights out/on

and times of removal of the actigraph, as well as hypnotic use. Detailed verbal and written instructions will be provided prior to the assessments. Study materials will be delivered directly through home visits, overnight mail, or handed directly to the study participants at the time of the study sessions, depending on the time frame.

c. Potential Risks

1. Potential risks and their likelihood

Because study participants will engage in group discussions, there is some possibility that others in the group may disclose information to outsiders that may be confidential. The interveners will establish strict guidelines and rules for each group session to discourage disclosure outside of the group setting. Participants will be asked to enter their daily weights, symptoms, sleep and practice of skills learned in an electronic log. They will also be asked to complete an electronic sleep diary prior to the intervention and at each of the 5 data collection periods. The electronic logs will be included as links on password protected and encrypted mini-tablet computers. These data can be uploaded directly by the participants to Yale's HIPAA compliant website or completed offline and uploaded when WIFI is available. However, due to password protection and encryption, the risk of a violation of privacy is minimal. If participants decide to use their own electronic devices (smart phone, computer, tablet), the log data will not reside on the device, but will be directly entered onto the Yale site with a password. It will not be possible to view data submitted by other participants. We will provide video-recordings of intervention sessions (HH and HS), but these will not be recorded with identifiable study participants.

Risks are highly unlikely. However, stimulus control therapy, a component of CBT-I requires the patient to get out of bed when sleepy. For frail patients, it is possible that this could result in falls. Sleep restriction may result in excessive daytime sleepiness and lower the seizure threshold for people who have undiagnosed epilepsy or bipolar disorder. However, we do not expect this to occur, as these are exclusion criteria. In addition, paradoxical anxiety reactions have rarely been reported as a result of relaxation therapy. It is possible, but unlikely that the group sessions, telephone calls, or interviews may elicit psychosocial distress in study participants. The clinicians leading the sessions include experienced advanced practice nurses who will refer participants for follow-up care as appropriate.

We may uncover sleep disordered breathing or psychiatric disorders, such as depression in the screening process. Participants with these conditions will be notified and suggestions will be made for follow-up care. All patients and referring providers will receive a written report of their sleep evaluations and depressive and anxious symptoms with recommendations for follow-up as needed. We will not send these reports to providers other than those referring to the trial because that would be a HIPAA violation. If our screening suggests that any patient may be suicidal, we will refer them immediately for follow-up.

2. Alternative Treatment

An alternative treatment for study participants is the use of hypnotic drugs. Other forms of behavioral treatment are available that include components similar to those in this study (relaxation, sleep restriction, sleep hygiene, etc.). Patients who are depressed or anxious and have insomnia may also benefit from pharmacological or behavioral treatment for these conditions. However, several studies have shown that CBT-I improves mood disorders with and or without additional pharmacological treatment.

Adequacy of Protection Against Risks

a. Recruitment and Informed Consent

1. Recruitment

Participants will be recruited through the Yale-New Haven Hospital (YNHH) Heart Failure and Transplantation Center, and the VA CT Health Care System. We will also have access to the Yale Primary Care Center. We will place brochures and/or posters in medical offices and post information on the Yale CTSA website to provide information about the study and with a telephone number to contact the study coordinator. In addition, the clinicians in these practices will identify potential participants during routine care, briefly explain the study and elicit their permission to be contacted by a member of the study team. The research coordinator will meet with potential study participants and explain the study in detail, answering questions. Written information will be provided. We will also screen medical charts and sent invitation letters by mail. Epic MyChart will also be used to identify and notify potential candidates for the study. Patients who have an Epic MyChart account and meet basic inclusion /exclusion criteria will be notified of the study through a MyChart message. The online

recruitment tool “Research Match” will be used to advertise the study, along with Yale websites. All recruitment methods will be approved by Yale University Human Investigations Committee (IRB).

2. Consent procedure
The study research coordinator or research assistant will obtain consent. After explaining the study procedures, all risks and benefits, as well as alternative treatments, protection of confidentiality and contact information for the IRB, participants will be provided a written informed consent document to read. If they prefer, the study personnel will read the document to them. Participants will sign 2 copies of the consent, retain one, and the researchers will keep the second copy on file. Potential participants will be told that HF self-management strategies provided in the attention-control condition may also improve their sleep, based on improvements in HF.

b. Protections against Risk
1. Procedures for minimizing risk
We will protect against the risks of the effects of the experimental condition by excluding patients who have bipolar disorder or seizure disorders, as well as those with Epworth Sleepiness Scale scores >18 due to the potential for sleep restriction to increase sleepiness and potential injury. In addition, we will not use sleep restriction below 4.5 hours to avoid extreme sleepiness. We will not include individuals with severe depression in either group. Participants will be carefully monitored for these and any changes in emotional distress, particularly anxiety and depression. The clinicians leading the groups are health professionals who are trained to observe for these issues. Participants will be instructed to call the research coordinator if they have worsening of their sleep, emotional distress, or increased severity of any symptoms over the course of the study. Participants will be referred to a mental health clinicians or the cardiology health care provider if they have any of these concerns. If new or exacerbated health problems, such as sleep apnea or depression, are detected during the study assessments, participants will be referred to their referring providers (or a provider of their choice) for follow-up evaluation and possible treatment.

All study participants and their referring health care providers will receive a report of their ARES sleep studies (measure of sleep disordered breathing) and a report of the depression screening with appropriate recommendations for treatment if indicated.

The risk of violation of confidentiality will be minimized by using documents with code numbers, linked only to the master list of participants that will be maintained in a physically locked file. Electronic records, including the patient logs, will be password protected and encrypted, consistent with Yale University policies. Only members of the study team will have access to the physical or electronic data.

Potential Benefits of the Proposed Research to Human Subjects and Others
a. Potential Benefits to Participants
Potential benefits include learning more about sleep and improving insomnia, as well as self-management of heart failure. It is also possible that symptoms, including sleepiness, fatigue, anxiety, and depression, and daytime functioning may improve, especially in the experimental arm. Participants in the comparison group will learn about self-management of heart failure, including increased understanding of the disease process, medications, fluids, diet, sodium management, stress management and exercise, as well as basic information about sleep. It is possible that improvement in these behaviors may improve sleep/insomnia, as well as symptoms and functional performance. HF self-management information will be available to both groups through the Fight against Heart Failure Handbook.

b. Balance of Risks and Benefits
The risks of this study are minimal relative to the potential benefits.

Importance of the Knowledge to be gained
The knowledge obtained in this study may lead to important advances in understanding the outcomes of cognitive behavioral therapy for insomnia, an efficacious treatment in many populations that has been under-studied among people with HF. Based on our preliminary work, we expect that CBT-I will reduce insomnia severity and lead to improvements and fatigue and possibly other symptoms related to insomnia and often experienced by HF patients. This study will also evaluate the impact of CBT-I on health care utilization and cost, as well as event-free survival. If, as we hypothesize, CBT-I has sustained efficacy and is cost-effective,

this study will provide critical evidence to support of future translational work in which we will conduct an effectiveness study focused on enhancing reach, adoption, implementation, and long term maintenance[65] (factors associated with sustainability) of CBTI-into diverse HF disease management settings. For example, this study may include structured online training for HF registered nurses; education on use of acceptable billing codes for insomnia and fatigue treatment; and strategies to integrate CBT-I into cardiac rehabilitation programs or HF support groups, among others.

Data Safety and Monitoring Plan
The risks are very minimal in this single-site study, therefore a data and safety monitoring board is not required.[200] We had no adverse events in our previous study.

a. Monitoring entity or who will monitor the study (i.e., PI, ISM, SMC, or DSMB).
The PI will have primary responsibility for overseeing all aspects of the study, including compliance with all human subjects requirements, ongoing monitoring for adverse events, and submitting reports to the Yale IRB and NINR. An Adverse Events Committee, comprised of the PI, a senior scientist with expertise in symptom management from the school of nursing and a physician sleep specialist will review all possible adverse events and make recommendations. Aside from the PI, neither of the other 2 members will be affiliated with the study. The PI will report the following to NINR: Unanticipated problems or unexpected serious adverse events that may be related to the study protocol; IRB-approved revisions to the study protocol that indicate a change in risk for participants; A summary of recommendations made by the Adverse Events Committee or other monitoring entity as appropriate and (if applicable) the action plan for response; Notice of any actions taken by the IRB or regulatory bodies regarding the research and any responses to those actions.

b. Procedures for 1) monitoring study safety to include monitoring schedule, auditing selected cases for compliance with IRB requirements, conformance with informed consent requirements, verification of source documents, and investigator compliance; 2) minimizing research-associated risk, and 3) protecting the confidentiality of participant data.

1) The PI will audit selected cases on a monthly basis for conformance with informed consent requirements; take responsibility for assuring the confidentiality of the data collected, verify the source documents, and submit reports to the NINR. The Adverse Events Committee will review all possible adverse events and make recommendations. The Adverse Events Committee will meet quarterly and as needed to review events related to the study. The PI will report adverse events promptly to this group and to the Yale University Institutional Review Board's Human Investigation Committee (HIC).

2) The PI will continuously monitor all study personnel, data and all study procedures to minimize research-associated risk and assure that personnel are adequately trained and follow procedures as per the human subjects research protection program. Specific strategies within the study protocol will include the following:

We will protect against the risks of the effects of the experimental condition by excluding patients who have bipolar disorder or seizure disorders, as well as those with Epworth Sleepiness Scale scores >18 due to the potential for sleep restriction to increase sleepiness and potential injury. In addition, we will not use sleep restriction below 4.5 hours to avoid extreme sleepiness. We will not include individuals with severe depression in either group. Participants will be carefully monitored for these and any changes in emotional distress, particularly anxiety and depression. The clinicians leading the groups are health professionals who are trained to observe for these issues. Participants will be instructed to call the research coordinator if they have worsening of their sleep, emotional distress, or increased severity of any symptoms over the course of the study. Participants will be referred to a mental health clinicians or the cardiology health care provider if they have any of these concerns. If new or exacerbated health problems, such as sleep apnea or depression, are detected during the study assessments, participants will be referred to their referring providers (or a provider of their choice) for follow-up evaluation and possible treatment.

All study participants and their referring health care providers will receive a report of their ARES sleep studies (measure of sleep disordered breathing) and a report of the depression screening with appropriate recommendations for treatment if indicated.

3) The risk of violation of confidentiality will be minimized by using documents with code numbers, linked only to the master list of participants that will be maintained in a physically locked file. Electronic records, including the patient logs, will be password protected and encrypted, consistent with Yale University policies. Only members of the study team will have access to the physical or electronic data.

c. Procedures for identifying, reviewing, and reporting adverse events and unanticipated problems to the IRB, NINR, and FDA (if applicable).

The PI will report adverse events promptly to the Adverse Events Committee and to the Yale University Institutional Review Board's Human Investigation Committee (HIC). The PI will report serious adverse events or deaths encountered during the study immediately by phone to the HIC and to the NINR. The PI will follow-up immediately to gather more information about the event. Additional information will be acquired as necessary. If the PI is unavailable, there will be an on-call schedule that includes the co-investigators who will follow-up in place of the PI.

d. For multi-site studies, procedures to ensure compliance with the monitoring plan and reporting requirements across study sites.

This is not a multi-site study.

e. An assessment of external factors or relevant information (e.g., developments in the literature, results of related studies) that may have an impact on the safety of participants or on the ethics for the research study.

To our knowledge there are currently no external factors or relevant studies that may have an impact on the safety of participants or on the ethics of the research study. The PI will continue to monitor the literature and reports of studies disseminated through other venues (e.g., conferences) throughout the duration of the study. If changes are indicated, she will discuss with the Adverse Events Monitoring Committee and with NINR staff.

f. **The advanced plans for interim and/or futility analysis as appropriate**.

Interim analyses will not be needed, as this is a low risk study. Conduct of interim analysis would introduce undue Type I error.

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Statistical Analysis Plan

Data Analysis. We will use Actiware v.6 software (Respironics Minimitter, Inc.) to score actigraph data. Personnel blinded to group assignment will use event markers, light meter and diary recordings to identify "lights on/out" and removal times and to summarize actigraph variables over the 2-week intervals. Use of three methods will minimize problems with missing data (e.g., occlusion of the light meter) for single indicators. Wrist-worn light meters are valid measures of ambient light.[193]

To identify outliers and data errors, we will use logical data checks and handle missing data with the assumption of missing at random (MAR), an approach that assumes missing values have the same patterns as complete data. We will impute missing data on survey items with Rubin's[194] multiple imputation method, replacing missing values with simulated sets of imputed values from Monte Carlo simulation, and analyze each simulated completed dataset with standard methods. Results will include estimates and confidence intervals that incorporate the uncertainty of imputed values. Generalized Linear mixed Models (GLM) and General Estimating Equations (GEE) allow the use of incomplete repeated measures due to dropout, If there is at least one baseline and follow-up data point. This approach will minimize the effects of sample loss due to attrition

We will compute univariate statistics to examine frequency distributions of categorical variables and normal distributions for continuous variables with box plots and the Shapiro Wilkes test to assess normality. We will test differences in demographic and clinical variables (e.g., SA, LVEF), and baseline adherence, self-care, and self-management (see inclusion/exclusion criteria; clinical/demographic variables) between the two randomized groups to determine the success of randomization. Because some clinical and demographic variables, including PAP use, may influence outcomes, we will include them as covariates in multivariate models if groups are unbalanced on these variables at baseline.

We will use descriptive statistics to describe clinical and demographic characteristics by treatment group and time. To evaluate differences in insomnia severity, sleep characteristics (Aim 1a), symptoms, PVT (Aim 1b) and functional performance (Aim 2) over the four time points (baseline, 3, 6, and 12 months), we will use GLMM with a repeated measures statement to examine group, time, and group by time effects. Nonlinear time effect will be controlled by transforming a continuous time variable with cube root form, which allows to estimate relatively rapid change in early at post-intervention than the follow-ups. We will choose the best covariance structure (compound symmetry vs. unstructured vs. moving average) by comparing the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). In multivariate models, adjusted intervention effects will be estimated by including covariates that might differ by group assignment (e.g., LVEF, comorbidity, age, SA with CPAP use). We will assess multi-collinearity among covariates with the variance inflation factor (VIF) and eliminate variables with high VIF (> 10) if the intervention effect is not modified after elimination. We will identify influential outliers with DFFITS, DFBETAS, and Cook's distance. If there are non-normally distributed residuals, the outcome variable will be transformed to ordinal form or fitted with more flexible distributions (e.g., Gamma, Poisson). We will use GEE with a robust working correlation structure to address within-subjects correlations for changes in outcomes with clinical cutoffs (i.e., ISI≥, ESS≥10, PSQI≥5, SMW≥1000) over time. To avoid the inflation of type 1 error, False Discovery Rate (FDR) will be calculated for post-intervention effects on 13 outcome variables. .

For cluster analysis (Aim 1c), we will use Latent Transition Analysis (LTA)[195,196] to produce a latent variable categorizing a symptom cluster at baseline and follow-ups. Consistent with methods in cardiac samples[166] each participant will be stratified into a symptom cluster group, based on dichotomized symptom severity. In our pilot, we found 3 clusters (I: mild); (II: high pain/dyspnea); (III: severe – high depression. anxiety, sleepiness). We expect LTA to produce two or more clusters of 2 or more symptoms characterized by symptom severity and patterns of correlated symptoms. LTA provides the item-response probability of having a specific symptom in each symptom profile group and the probabilities of membership in each symptom profile at each time and transitioning from one symptom profile to another. SEM and other similar latent variable methods do not quantify symptom cluster membership and transitions between clusters over time. The LTA model will include a group variable as a covariate to test the effects of CBT-I on membership in a symptom cluster and transition between clusters over time.

We will use GLMM or GEE to determine the extent to which the effects of CBT-I on insomnia, sleep characteristics, symptoms and functional performance 6, 9, and 12 months are non-inferior to outcomes at two weeks. (Aims 1a, 1b, 2). We will identify potential barriers to sustained intervention effects (e.g., LVEF, comorbidity, PAP treated SA, self-care/self-management) by testing interactions between time and covariates associated with outcomes.

To address Aim 3, we will perform stochastic cost-effectiveness analysis (CEA) from the perspective of society. We will document resource utilization in units for direct and indirect costs (above) 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 CEA is to estimate the incremental cost per additional unit of effectiveness, measured as QALYs, the standard in cost-effectiveness research and economic evaluations of sleep disorders.[101] We will estimate QALYs by applying the utility measure derived from the 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 summarize the cost-effectiveness of CBT-I relative to HH with an incremental cost-effectiveness ratio (ICER):

$$\mathbf{ICER} = \frac{C_{CBT-I} - C_{HH}}{E_{CBT-I} - E_{HH}}$$

(C_{CBT-I}: expected cost of the intervention; C_{HH}: expected costs for the HH group; $E_{CBT-I:}$ effectiveness of the intervention, measured as QALYs;E_{HH}: effectiveness in the HH group). ICER represents the incremental cost to gain an additional QALY with CBT-I. We will discount costs over the 3 years of data collection and estimate uncertainty around the ICER by bootstrapping, yielding a 95% confidence ellipse around the ICER. In the usual cost-effectiveness framework, a willingness to pay threshold is used to determine cost-effectiveness of a treatment. However, in a stochastic cost-effectiveness framework, we can estimate the probability that CBT-I is cost-effective over a wide range of willingness to pay thresholds with the cost-effectiveness acceptability curve (CEAC). We will perform sensitivity analyses for costs, life expectancy, and utility.

We will use survival analysis for exploratory aim 1 and compare time to EFS between CBT-I and the attention control condition with a competing risk approach.[197] This approach accounts for the relationship of the occurrence of one event with others. Participants who do not experience events during f/u will be right-censored. As a secondary analysis, we will examine time to specific events (e.g., hospitalization, death). We will adjust the survival model by including baseline Seattle Heart Failure score,[186] depression, LVEF, adherence,[36] and self-care/self-care management,[77] as they predicted EFS.