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Moderators of response to cognitive behavior therapy for major depression in patients with heart failure

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Abstract

Objectives: While cognitive behavior therapy (CBT) is efficacious for major depression in patients with heart failure (HF), about half of patients do not remit following CBT. This report sought to identify treatment moderators to help guide treatment allocation strategies and identify treatment targets. Based on plausibility and available evidence of their prognostic relevance, we evaluated whether clinical and activity characteristics moderate CBT's effect.

Methods: Participants were randomized to receive enhanced usual care (UC) alone or CBT plus enhanced UC. The single-blinded outcomes were six-month changes in Beck Depression Inventory (BDI-II) total scores and remission (defined as a BDI-II≤9). Actigraphy was used to assess daily physical activity patterns. We performed analyses to identify the specific activity and clinical moderators of CBT's effect in 94 adults with HF and major depressive disorder (58 years old on average).

Results: Patients benefited more from CBT (vs. UC) if they had: more medically severe HF (i.e., a higher NYHA class or a lower left ventricular ejection fraction), more stable activity patterns, wider active periods, and later evening settling times. Individual moderator effects were small, but combining the moderators yielded a medium moderator effect size (r=0.38; 95% confidence interval, 0.20, 0.52).

Conclusions: Activity patterns and clinical measures appear to moderate CBT's effects on depression in adults with HF. These findings suggest that stabilizing activity patterns and prolonging the daily active period might help increase CBT's efficacy. Research is needed to clarify and address the factors that diminish CBT's efficacy in patients with less severe HF.

Trial registration: clinicaltrials.gov identifier:

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When major depression and heart failure (HF) co-occur, as they often do[1,2], their individual associations with disability are amplified[3]. Successfully treating depression in people with HF is therefore a high priority. Unfortunately, randomized controlled trials (RCTs) have shown that standard antidepressant medications are not superior to placebo for major depression in people with heart failure[4–6]. In contrast, our team recently reported that an integrative intervention based on cognitive behavior therapy (CBT) was more efficacious than usual care (UC) for depression in people with heart failure[7]. Despite this success, about half of the patients assigned to CBT did not fully remit following treatment. The factors which determine whether CBT will be efficacious for a given patient, i.e., moderators of CBTs effects, are not well-established.

The distinction between moderators and general prognostic factors is clinically meaningful[8]. General prognostic factors are related to the course of an outcome (e.g., depression severity over a six-month follow-up period) regardless of treatment assignment. In contrast, moderators are associated with the efficacy of a specific treatment when compared with an alternative. Thus, evidence regarding treatment moderators can help clinicians identify whether a given patient is likely to benefit from a particular treatment. Furthermore, it may be possible to modify certain moderators that predict diminished efficacy in order to prime subgroups of patients for treatment. However, most prior research on moderators of CBT has focused on non-modifiable moderators such as age or sociodemographic factors[9], and there has been little moderator research specific to CBT in patients with HF. Our prior publication demonstrating CBT's efficacy for patients with depression and HF did not find evidence for moderating effects of sex, race, or antidepressant use[7].

We therefore performed a wider but targeted search for moderators of CBT's effects in patients with HF. To target this search, we relied on past evidence regarding the role of physical activity as a general prognostic factor in depression. Low activity levels[10] and activity rhythm disruption[11] are known depression risk factors. Among patients given standard psychotherapy, people with lower levels of physical activity tend to experience a worse prognosis over time[12]. However, this prior work did not address whether activity characteristics moderates CBT response, and was limited by reliance on a self-report physical activity measure. There are several other easily obtainable measures of physical functioning and activity including clinic-based test performance measures and objectively measurable activity characteristics (e.g., average activity levels, activity pattern stability, and activity timing). Since these measures can be easily obtained, e.g., from passive accelerometer-based technology, they could be assessed clinically to help guide treatment strategies.

If any aspect of physical functioning in this group (e.g., HF characteristics, clinic-based functional measures, or accelerometry-based measures) moderate CBT's effects, this would highlight the need to address these factors as a part of depression treatment. Therefore, our first aim was to evaluate individual moderator effect sizes. However, individual moderator effects tend to be small and can provide conflicting treatment indications[8]. Past work has shown that combining multiple moderators can yield larger, more clinically meaningful effects[13,14]. Therefore, our second aim was to assess the effect size gains achieved when combining information from multiple individual moderators.

Methods

Participants

The methods and major outcomes of the trial were reported in an earlier publication[15]. Briefly, patients with heart failure were enrolled at the Washington University Medical Center in Saint Louis, Missouri between January 4, 2010 and June 28, 2013. Inclusion criteria were: New York Heart Association (NYHA) Class I-III heart failure diagnosed three or more months before screening, current major depressive episode[16], and a score of 14 or more on the Beck Depression Inventory (BDI-II)[17]. Exclusion criteria were: being unable to participate because of cognitive impairment, frailty, a communication deficit, or a logistical barrier; poor 1-year prognosis due to a noncardiac comorbidity; past month hospitalization; past month, suicidality, psychosis, or substance abuse; and antidepressant initiation in the past eight weeks (patients treated with antidepressants for more than eight weeks were included). Written informed consent was obtained and participants were compensated for participation. The study was approved by the Washington University Medical Center Human Research Protection Office. One hundred fifty-eight participants were randomized. The present analyses include participants who had data on the six-month depression outcomes (n=123) and are further restricted to 94 patients in whom the baseline moderators were measured (as specified below).

Randomization

Participants were randomly assigned, in a 1:1 ratio, to CBT plus enhanced UC or enhanced UC alone. Randomization was stratified by baseline antidepressant use.

Interventions

The intervention was described previously[7]. Briefly, both groups received enhanced UC, which consisted of educational materials on HF self-care from the Heart Failure Society of America[18] and the American Heart Association[19]. Educational materials were reviewed on three 30-minute telephone calls with an experienced cardiac nurse conducted over three to four weeks post-randomization. The CBT group additionally received up to six months of treatment following standard CBT manuals[20,21] as well as a supplemental manual on CBT for cardiac patients[22].

Outcome measures

Baseline assessments were conducted between February 2010 and April 2013, and follow-up assessments were collected between May 2010 and July 2014. Outcome assessors were blinded to group assignments. The depression outcome was defined as symptom reductions on the BDI-II[17] (defined as six-month scores minus baseline scores; with negative numbers indicating symptom reductions). To clarify the clinical significance of our findings, we also evaluated how the full combined moderator related to remission status at six months (defined as a score of nine or less on the second version of the Beck Depression Inventory (BDI-II)[15,17].

Potential moderators

All moderator measures were assessed at baseline. New York Heart Association (NYHA) class I-II vs. III was used to assess the severity of HF symptoms and left ventricular ejection fraction (LVEF) obtained from echocardiography was used as an index of left ventricular function. Physical functioning was measured as the PROMIS Physical Functioning score[23] and distance (in feet) walked on the 6-minute walk test[24].

Participants also wore tri-axial accelerometers (Philips Respironics Inc., Murrysville, PA) at baseline to collect minute-by-minute activity counts for one week. We applied both nonparametric[25] and extended-cosine[26] methods to quantify activity characteristics. From the nonparametric measurements, we assessed the level of activity (the average amount of activity during the most active ten hours or M10), rhythm strength (the relative amplitude or RA defined as the difference, between the average levels of activity during the most active 10 hours of the day and the least active 5 hours of the day, standardized to overall activity level), rhythm stability (interdaily stability or IS defined as the ratio of variability within the mean 24-hour activity profile to the overall activity variability), and rhythm fragmentation (intra-daily variability or IV defined as the ratio of the hour-to-hour activity variability to the overall activity variability). We also used a sigmoidally transformed cosine curve to estimate alpha (a parameter indicating the relative width of active to rest periods with higher values indicating more narrow active relative to resting periods) and two timing parameters (reflecting the times when activity levels pass through the middle level of the estimated model when the participant “gets going” (up-mesor) and “settles down” (down-mesor)).

We analyzed actigraphy data only from adequate recordings defined as those with a duration of at least 72 hours of data; 18 recordings did not meet this criterion (analytic sample reduced to n=105). Extended cosine modeling did not converge for an additional eight patients who were therefore excluded (analytic sample reduced to n=97). Of these participants with complete outcome and actigraphy data, three did not have data from the walk test and were excluded. The resulting 94 patients who were included did not differ from those missing moderator measures in terms of gender (Chi square test p=0.40), treatment assignment (Chi square test p=0.75), baseline depression (Chi square test p=0.30), symptom changes (T-test p=0.10), or remission status (Chi square test p=0.27).

Statistical analysis

We computed individual moderator effect sizes and 95% confidence intervals (CIs) using bootstrapping[8]. Effect sizes are based on Spearman correlations, with more positive values indicating that greater values of the moderator are associated with less benefit of CBT over UC; more negative values indicating that greater values of the moderator are associated with more benefit of CBT versus UC.

Next, we assessed moderator effect sizes when combining clinic-based measures, accelerometer-based measures, or both. Only measures with individual moderator effect sizes of $\geq|0.10|$ were considered potentially relevant and included the combined moderator models. The combined moderator method derives optimal weights for each moderator through a LASSO regression, which allows for correlated variables without overfitting[27].

LASSO weights are extracted and applied to the original data to compute a combined moderator. We then estimated the combined moderator effect sizes (95%) CI. To illustrate the combined moderator effects, we plotted the combined moderators against the predicted level of depressive symptom change in each of the treatment arms. To assess how the full combined moderator related to remission, we calculated the odds of remission given CBT (vs. UC) in people who were above and below the "cross-point" (see below). These odds ratios were calculated using logistic regression adjusted for age, sex, and antidepressant use. For all analyses, continuous variables were standardized to a mean of 0 and standard deviation of 1.

Results

Individual moderators effect sizes (Table 2 and Figure 1):

The absolute values of the individual moderator effect *s*izes were small (range: r=0.00 to 0.21). The largest moderator effect sizes from the clinic-based measures were percent LVEF and NYHA class III vs. I/II. Lower LVEF values, indicating worse cardiac contractile function, were associated with a greater effect of CBT vs. UC on depression symptom change. Patients in NYHA class III, indicating more severe heart failure symptoms (vs. NYHA grades I/II), also benefited more from CBT.

Of the actigraphy variables, interdaily stability, alpha, and down-mesor had the largest moderating effects. More regular activity patterns across days (higher interdaily stability) was associated with a greater effect of CBT. Having narrower active periods (higher alpha) was associated with less benefit from CBT. Later evening settling times (later down-mesor) was associated with a greater effect of CBT.

Combined moderator effect sizes (Table 2 and Figure 2):

When combining the moderators within the clinic and actigraphy variable sets (separately) effect sizes were still small. In contrast, the full combined moderator that included both clinic-based and actigraphy measures yielded a medium moderator effect size.

Relationship between the full combined moderator and remission:

We stratified patients depending on whether they were above or below point where the lines cross in the full combined moderator (right of Figure 2; above the cross-point, the effects of CBT and UC are similar, whereas below the cross-point CBT is associated with larger symptom reductions). In patients below this cross-point (76% of the sample), CBT was associated with a greater likelihood of remission when compared with UC (see Figure 3); in this subset of patients, the odds ratio for remission for CBT vs. UC was 5.0 (95% confidence interval: 1.78, 14.1; p=0.002). In contrast, in the 25% of patients who were above this cross-point, remission rates were similar in the CBT and UC arms; in these patients, the odds of remission for CBT vs. UC was 0.88 (95% confidence interval: 0.11, 6.93; p=0.90).

Discussion

Consistent with other studies[13,14], we observed that the moderating effects of individual patient characteristics were generally small. However, combining information from individual variables yielded a moderate effect size and identified a subgroup of patients who were unlikely to remit regardless of whether they were provided with CBT or UC alone (Figure 2). Pending replication, these clinical and actigraphy variables could be routinely assessed prior to treatment and combined to assess the likelihood that any given patient will benefit more from CBT than UC. When treating patients with high combined moderator scores, clinicians could consider the factors that led to high combined moderator values, and explicitly address them during treatment. We are not suggesting that, in practice, CBT should be withheld from patients with high moderator scores; rather, we propose that it may be possible to pre-empt non-response to CBT by identifying patients who are less likely to benefit and then addressing barriers to treatment success early on.

Surprisingly, we found that the benefit of CBT vs. UC was larger in patients with indicators of more severe HF. In contrast to the medical prognosis for patients with HF and reduced ejection fraction, the prognosis for patients who have HF with preserved ejection fraction has not improved in recent decades[28]. HF with preserved ejection fraction may have a more complex pathophysiology that may be more challenging to treat[29]. Thus, patients who had a reduced ejection fraction may have experienced less uncertainty, frustration, or disappointment with the medical management of their heart failure, whereas difficulties managing HF with preserved ejection fraction may have contributed to a lack of benefit when provided CBT. Although empirically testing this explanation represents a next step outside the scope of this work, our novel findings suggest that future studies and treatments may need to consider the trajectories of physical health a potential barrier or facilitator of depression remission in patients with HF.

Our second set of findings pertained to baseline physical activity variables that are associated with CBT's efficacy. We found that the effect of CBT over UC was smaller in patients who had less stable activity patterns and narrower active periods at baseline, likely due to earlier evening settling. These activity characteristics have been previously associated with depression symptoms, e.g., studies examining the stability of activity patterns across days[30,31] and the active period length[31–34]. Unstable activity patterns and narrower active periods may reflect less regular and consistent engagement with rewarding social and leisure-time activities. Unstable activity patterns could also reflect the burden of comorbidities or circadian misalignment (e.g., poor coordination between the timing of biological and/or psycho-behavioral processes). Future work is needed to clarify why these aspects of activity patterns are associated with depression[30–34] and a lack of benefit when given CBT vs. UC. Prior research has shown that bright light therapy[35,36] and exercise[37] can stabilize activity rhythms, and it is plausible that activity planning occurring in CBT could deliberately prolong the active period. Future work will need to test whether adjunctive or primer treatments (e.g. home-based cardiac rehabilitation) aimed at stabilizing activity patterns and prolonging the active period can facilitate greater CBT efficacy.

Several limitations should be noted including, as stated above, our inability to specify precisely why these factors predict greater or lesser CBT efficacy. In addition, our sample size was relatively small and we did not have adequate statistical power to detect small moderation effects. We focused on effect sizes rather than p-values; however, given that this is the initial work examining the moderating role of activity characteristics, our findings must be validated before clinical implementation. Another potential limitation is that this trial was conducted in a specialty care setting; as such, our findings may not generalize to primary care settings where other moderators may emerge.

Despite these limitations, our study has several strengths. First, we used a randomized controlled trial to identify moderators of an established, but not uniformly efficacious, treatment in an chronically ill patient population. Second, we assessed clinical and actigraphy-based variables that are at least theoretically feasible to routinely assess in this clinical context. Third, using a combined moderator methodology rendered a more meaningful (larger) effect size and identified a group in whom CBT and UC were equally efficacious.

In conclusion, we have demonstrated the utility of the combined moderator approach and identified objectively measurable factors that could be addressed to clarify why CBT is more efficacious for some patients with major depression and HF than it is for others. Our findings regarding the severity of heart failure highlight the need for psychological treatments to acknowledge the challenges facing patients who have heart failure with preserved ejection fraction. We also generated initial evidence regarding which baseline activity characteristics that are relevant to CBT's efficacy. These moderating patient characteristics that apparently detract from/are required for CBT's efficacy should be addressed in future work. Potentially, considering and/or modifying these pre-treatment moderators could better prepare patients for success in CBT.

Conflict of Interest and Source of Funding:

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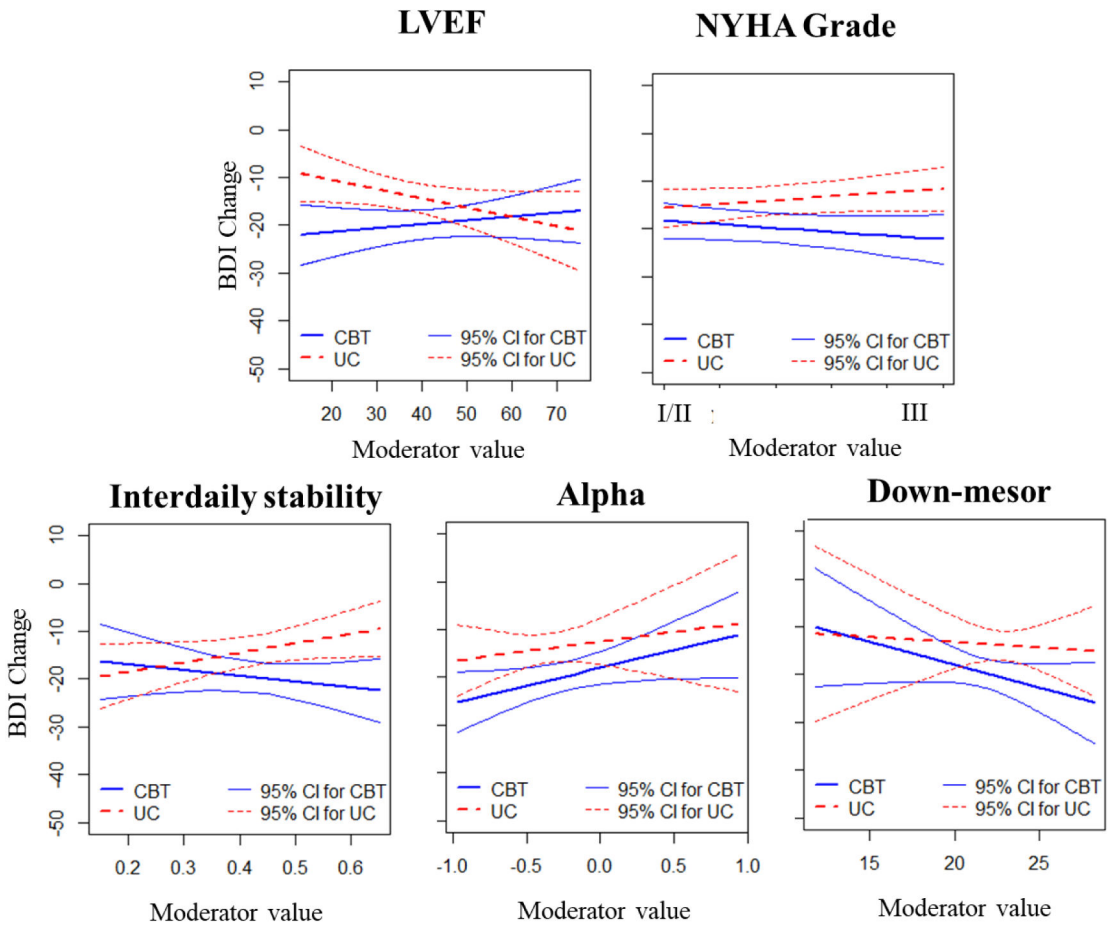

Figure 1. Average depression symptom changes in the two treatments depending on the value of the indiviudal moderators.

Note the difference between the two treatment arms in terms of the level of depression symptom changes varies across the moderator values, e.g., there is less overlap between the two lines at lower values of LVEF and higher values NYHA grades.

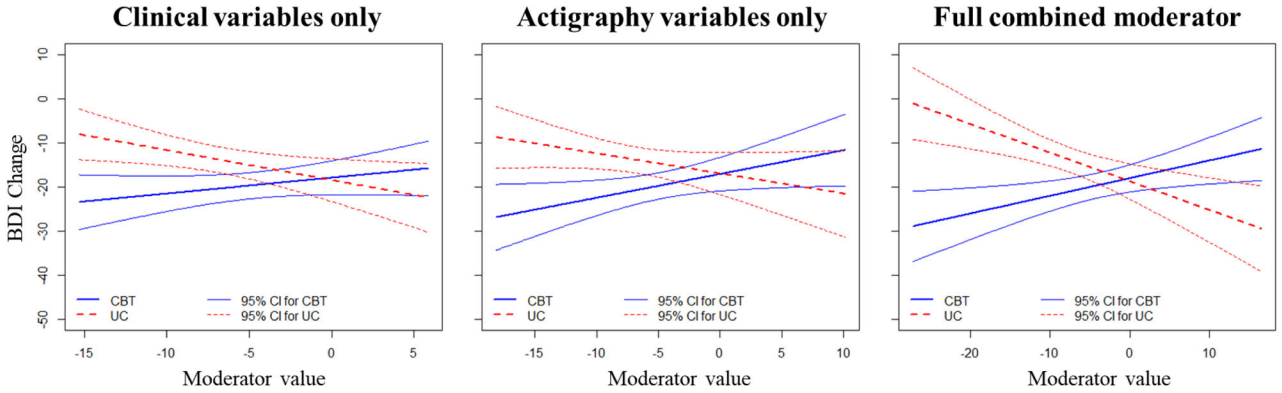

Figure 2. Average depression symptom changes in the two treatments depending on the value of the combined moderators.

Note that CBT-UC separaton is greatest at lower values of the full cominbed moderator.

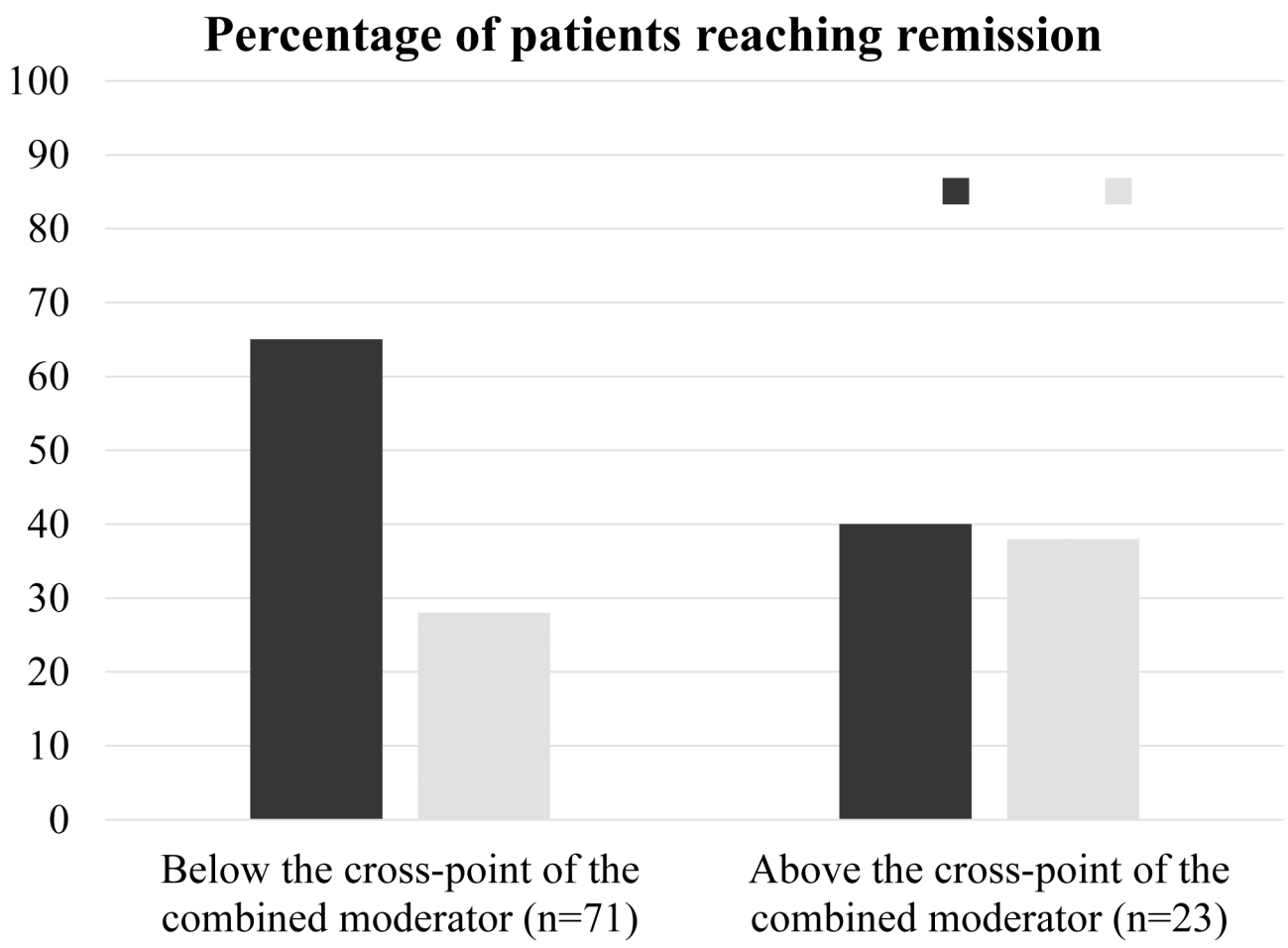

Figure 3. Remission rates stratified by treatment arm and the cross-point of the full combined moderator.

Table 1.

Baseline descriptive information from the analytic sample

	CBT (n=46)	UC (n=48)
Age	58 (11)	58 (11)
Female, % (n)	52 (24)	46 (22)
Baseline BDI-II	30 (7)	30 (9)
BDI-II change (6 month-baseline)	−20 (11)	−14 (10)
Remission, % (n)	56 (26)	29 (14)
Potential moderators		
PROMIS Physical Function	37 (7)	35 (6)
6-minute walk test distance (feet)	1006 (391)	988 (444)
Percent LVEF	43 (17)	37 (15)
NYHA Grade III	35 (16)	44 (21)
Average activity during the most active 10 hours	208 (91)	238 (115)
Relative amplitude	0.8 (0.1)	0.9 (0.1)
Interdaily stability	0.4 (0.1)	0.4 (0.1)
Intradaily variability	1 (0.3)	1 (0.3)
Alpha (relative narrowness of active period)	−0.2 (0.4)	−0.3 (0.3)
Up-mesor	8 (3)	8 (2)
Down-mesor	22 (3)	23 (2)

Means and standard deviations shown unless otherwise noted; remission is defined as Beck Depression Inventory (BDI-II) scores of nine or less at the six-month follow-up

Table 2.

Individual and combined moderator effect sizes (n=94)

	Individual moderator effect sizes (95% Confidence Interval)
	BDI Change
PROMIS Physical Function	0.01 (−0.16, 0.19)
6-minute walk test distance (feet)	0.05 (−0.14, 0.23)
LVEF, %	**0.18 (0.01, 0.37)**
NYHA Grade III vs. I/II	**−0.19 (−0.37, 0.02)**
Average activity during the most active 10 hours (M10)	0.00 (−0.21, 0.18)
Relative amplitude	−0.09 (−0.28, 0.08)
Interdaily stability	**−0.21 (−0.39, −0.03)**
Intradaily variability	0.00 (−0.19, 0.22)
Alpha (relative narrowness of active period)	**0.13 (−0.07, 0.34)**
Up-mesor	0.03 (−0.15, 0.22)
Down-mesor	**−0.10 (−0.31, 0.08)**
	Combined moderator effect sizes (95% CI)
1. Clinical variables (LVEF % and NYHA class)	0.26 (0.08, 0.44)
2. Activity rhythm variables (interdaily stability, alpha, and down-mesor)	0.26 (0.05, 0.45)
3. Both clinical and activity rhythm sets (1 and 2 combined)	0.38 (0.20, 0.52)

Positive moderator effect sizes indicate that, as the value of the moderator goes up, the effect of CBT (vs. UC) is smaller; negative moderator effect sizes indicate that, as the value of the moderator goes up, the effect of CBT (vs. UC) is greater. Bold indicates the individual variable was selected into the combined moderator based on having an effect size of >0.10.