Stepped Care for Depression in Heart Failure (DASH-2) Trial

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STATISTICAL ANALYSIS PLAN FOR THE PRIMARY OUTCOMES MANUSCRIPT

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Overview

This manuscript will report the primary outcome analyses for the RCT. The primary research question is whether treating depression in patients with HF and comorbid major depression *before and while* intervening in HF self-care improves depression and facilitates better self-care outcomes. Participants were randomized to cognitive behavior therapy (CBT) for depression or to usual care for depression. The intervention was provided by mental health professionals. Starting at 8 weeks after randomization, all participants received a tailored self-care intervention (TSC), provided by a cardiac nurse.

Primary Outcomes:
(1) Beck Depression Inventory (BDI-2) at 16 weeks (end of intensive CBT phase)
(2) Self-Care of Heart Failure Index (SCHFI v6.2) Maintenance scale at 16 weeks (end of intensive TSC phase)

Interpretation rules: (1) If CBT is superior on the BDI-2 at 16 weeks, the intervention is efficacious for depression. (2) If CBT is superior on the SCHFI at 16 weeks, pre-treatment for depression improves self-care outcomes, regardless of whether CBT is superior to UC for depression. (3) If CBT is not efficacious for depression, the sequential treatment approach will not be recommended for clinical use even if patients in the CBT arm have better self-care outcomes.

Secondary Outcomes:
(1) Beck Depression Inventory (BDI-2) at 8 weeks (level of depression at start of TSC intervention)
(2) Beck Depression Inventory (BDI-2) at 32 weeks (CBT maintenance phase)
(3) Hamilton Rating Scale for Depression (HAM-D-17) at 16 weeks
(4) Self-Care of Heart Failure Index (SCHFI v6.2) at 32 weeks (TSC maintenance phase)
(5) Beck Anxiety Inventory (BAI) (8, 16, 32 weeks)
(6) Kansas City Cardiomyopathy Questionnaire (KCCQ) (8, 16, 32 weeks)

Exploratory Outcomes:
(1) Post-randomization recommendations and referrals for care outside of study
(2) Post-randomization non-study co-interventions for depression and heart failure

Descriptive Data:
(1) Sociodemographic data
(2) Baseline medical data
(3) Treatment Process Data log (CBT)
(4) Tailored Self-Care (TSC) visit form
(5) Blinding Assessment Follow-up Form (BAFF)

Statistical Analysis Plan for Primary Outcomes Manuscript

Data Preparation: Following the intention-to-treat (ITT) principle, we will use multiple imputation to impute data that are plausibly missing at random on all primary and secondary outcomes. $k \geq 25$ multiply-imputed datasets will be generated.

Screening and Baseline Data: We will create a CONSORT diagram to describe the numbers screened, enrolled, randomized, and analyzed, along with identification of reasons for attrition. We will generate Table 1 with demographic and medical variables for the enrolled sample as a whole and with Chi-square and ANOVA comparisons by group.

Primary Hypothesis Tests: The first co-primary hypothesis is that the CBT arm is superior to the UC comparison arm at 16 weeks on the Beck Depression Inventory (BDI-II). This will be tested by fitting the BDI-II scores at 8, 16, and 32 weeks to a linear mixed model (LMM). These scores (YBDI) will be regressed on time (βTIME), group (βGRP), baseline antidepressant stratum (βAD), baseline depression severity (βBDI), and the treatment x time interaction (βINT). The hypothesis will be tested by a contrast at 16 weeks (H0: μSCD=μUC vs. H1: μSCD≠μUC). Contrasts at 8 weeks (start of tailored self-care (TSC) intervention) and 32 weeks (end of maintenance phases of CBT and TSC) will be conducted as secondary analyses.

The power analysis for this analysis was based on a minimum clinically important difference (MCID) of $\geq$5.0 points between the groups at 16 weeks. This is larger than the 2-3 point MCID that has been established for some depression treatment studies, but we anticipated that a difference in depression of at least 5 points would probably be necessary to, in turn, achieve a significant between-group difference in HF self-care outcomes.

The second co-primary hypothesis is that the CBT arm is superior to the UC comparison arm at 16 weeks on the Self-Care of Heart Failure Index (SCHVI v6.2) Maintenance scale. The LMM analysis for this hypothesis is similar to the primary BDI-II analysis. An increase over baseline of approximately 8 points is considered to represent a clinically significant improvement, and a score $\geq$70 is considered to represent adequate self-care. As with the BDI-II, a secondary contrast will be conducted at 8 weeks (start of TSC intervention) and at 32 weeks (end of the maintenance phases of CBT and TSC).

Additional analyses of the BDI-II and SCHFI outcomes will incorporate covariables to evaluate the effects of "dosage" factors (i.e., number of sessions completed) and post-randomization co-interventions outside of the study (e.g., non-study psychiatric medications). Planned moderator or subgroup analyses will evaluate whether the effects of treatment differed by sex, race, age, baseline severity of depression, or antidepressant use.

Secondary Analyses: A series of analyses will be conducted to evaluate secondary outcomes:

1. Hamilton Rating Scale for Depression (HAM-D-17) at 16 weeks. (The HAM-D-17 was obtained only at baseline and Week 16).
2. Remission on the BDI-II (score <10) and on the HAM-D-17 (score $\leq$7) at 16 weeks, analyzed via logistic regression.
3. Self-Care of Heart Failure Confidence and Management scale scores at 8, 16, and 32 weeks.
4. Beck Anxiety Inventory (BAI) at 8, 16, and 32 weeks, analyzed via LMM similar to the primary analysis.
5. Kansas City Cardiomyopathy questionnaire at 8, 16, and 32 weeks, analyzed via LMM similar to the primary analysis.