Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods 1. Physiologic assessments

Procedures to Assess Aerobic Capacity, CVD Biomarkers, and Sympathetic Nervous System Activity

Aerobic Capacity. Graded treadmill exercise testing was conducted before and after treatment to document patients' aerobic capacity. Patients exercised to exhaustion or other standard endpoints under continuous electrocardiographic monitoring at workloads that were increased at a rate of 1 metabolic equivalent/min in accordance with the Duke-Wake Forest protocol. Expired gases were analyzed continuously using a Parvo Medics True One measurement system (Parvo Medics, Sandy, Utah).

Baroreflex sensitivity (BRS). Beat-by-beat blood pressure and heart rate were recorded for 15 minutes under supine fasting conditions using the Nexfin noninvasive BP monitor (Bmeye, Amsterdam, Netherlands). The last 5-minute segment of this recording was then edited for artifacts and linearly interpolated at a frequency of 4 Hz. A fast Fourier transform was applied to the interpolated data after detrending and application of a Hanning filtering window. Power spectra were derived using the Welch algorithm, which ensemble averages successive periodograms. Averages were derived from spectra estimated over nine 60-second data segments, overlapping by half. For each 60-second segment, 256 points were analyzed, which included 240 sampled points with zero padding. Baroreceptor-mediated adjustments in R-R intervals (defined as the reciprocal of heart rate) occurring across the low-frequency band (0.07 to 0.1299 Hz) were estimated from the magnitude of the transfer function relating R-R interval oscillations to systolic blood pressure oscillations. Coherence between SBP and R-R interval oscillations was required to be at least 0.5 in order to be accepted as estimated of BRS.

Heart Rate Variability. To quantify heart rate variability (HRV), an electrocardiogram

was recorded for 24-hours using the 3-channel DigiTrak XT Holter recorder (Philips Healthcare, Andover, Massachusetts). Electrocardiographic data were downloaded and edited using the Philips Zymed Holter analysis software (2010 Plus/1810 series) and HRV was estimated from the standard deviation of the normal-to-normal R-R intervals (SDNN).

Endothelial Function. Endothelial function, as assessed by Flow-Mediated Dilation (FMD), was measured using longitudinal B-mode ultrasound images of the brachial artery, 4 to 6 cm proximal to the antecubital crease. Images were obtained using an Acuson (Mountain View, California) Aspen ultrasound platform with an 11-MHz linear-array transducer. Images were obtained after 10 min of supine relaxation and during reactive hyperemia, induced by the inflation of a forearm pneumatic occlusion cuff to suprasystolic pressure (about 200 mm Hg) and subsequent deflation after 5 min. FMD was defined as the maximum percentage change in arterial diameter relative to resting baseline from 10 to 120 s after deflation of the occlusion cuff.

Urinary Catecholamines. Urinary catecholamines, an index of sympathetic nervous system (SNS) activity, has been shown to be positively correlated with anxiety. Urinary concentrations of epinephrine (EPI) and norepinephrine (NE) were determined by high-pressure liquid chromatography (HPLC) with electrochemical detection (LabCorp, Raleigh NC). Catecholamine levels were expressed as urine concentration (ng/mL) per urine concentration of creatinine (mg/mL), yielding NE and EPI values in ng/mg (adjusted for creatinine) for each sample.

eMethods 2. Data analyses

All analyses were carried out using SAS 9.4 (Cary, NC). Analyses of treatment group differences were carried out using general linear models, with group contrasts as factors, and ethnicity, age, sex, history of MI, presence of a diagnosed Anxiety Disorder, and the pre-treatment measure of the outcome variable as the adjustment covariables. For the case of the primary outcome, HADS-A, the model included post-treatment HADS-A score as the response, with the predictors including two *a priori*, pre-planned contrast variables representing 1) the two active treatments (exercise and escitalopram) vs placebo and 2) exercise vs escitalopram. To assess weekly changes in anxiety symptoms, STAI-S was analyzed using a repeated measures mixed model (PROC MIXED) with the same covariates as above. Time (week) was also included within this model, participant was modeled as a random variable, and an unstructured error structure was specified. We also examined a priori interactions between treatment, time (week), and baseline anxiety severity within our repeated measures analyses. In order to control for multiple comparisons, for secondary analyses of ancillary anxiety measures we used a unit-weighted composite score in which all secondary anxiety subtests were combined into a z-score at both pre- and post-treatment. The intent-to-treat principle was followed in all models, with missing data handled using multiple imputation through SAS (PROC MI).

eResults. Missing data

We found that our data were consistent with assumptions supporting the use of MI approaches (Cro S, Morris TP, Kenward MG, & Carpenter JR (2020). Sensitivity analysis for clinical trials with missing continuous outcome data using controlled multiple imputation: A practical guide. *Statistics in Medicine; 39:1-28*) and we found that the reported findings were not substantively changed when analyzed using alternative imputation approaches, including last observation carried forward. For example, data were analyzed to determine if using LOCF altered the pattern or significance of the findings. There were no substantial differences in the pattern of findings across the anxiety, fitness, and mechanistic outcomes. Post-treatment HADS-A levels were lower for active treatment groups compared to controls (P = .020) and lower in Escitalopram compared to Exercise (P <.001), with post-treatment levels of 3.5 (2.8, 4.2) for Escitalopram, 5.4 (4.7, 6.2) for Exercise, and 5.9 (4.8, 7.0) for Placebo. Examination of changes in aerobic fitness demonstrated a similarly robust pattern, with improvements in treatment groups compared to controls (P = .042) and in Exercise compared to Escitalopram (P = .002). Post-treatment VO_2 levels in LOCF analyses were 19.8 ml/kg/min (19.3, 20.3) in Exercise, 18.6 ml/kg/min (18.2, 19.1) in Escitalopram, and 18.4 ml/kg/min (17.6, 19.1) in Placebo controls. Finally, the pattern of improvements in urinary catecholamines paralleled our primary findings. Changes in norepinephrine differed between active treatment groups and control participants (P = .019) but not between Escitalopram and Exercise (P = .125), with post-treatment levels of 33.4 (30.6, 36.1) in Escitalopram, 36.5 (33.6, 39.3) in Exercise, and 40.5 (36.3, 44.7) in Placebo controls. Changes in epinephrine also paralleled the primary analyses, with post-treatment values of 3.4 (2.7, 4.0) in Escitalopram, 4.3 (3.7, 5.0) in Exercise, and 4.7 (3.8, 5.6) in Placebo (P = .115 for active treatment vs control; P = .033 for Escitalopram vs Exercise). Changes in secondary anxiety

measures on a mean rank composite also paralleled the primary findings, without significant

differences between active treatment groups and Placebo controls (P = .239) and greater

improvements in Escitalopram vs Exercise (P = .008).

eTable 1. Cardiopulmonary exercise parameters pretreatment and posttreatment

Variable	Aerobic Exercise	Escitalopram	Placebo	Contrast 1: exercise / escitalopram vs placebo	Contrast 2: exercise vs escitalopram
Peak VO$_2$ (ml/kg/min)				.019	.007
Pre	19.8 (6.3)	18.0 (5.2)	18.4 (4.2)		
Post	20.9 (6.5)	17.7 (5.3)	17.1 (3.5)		
Duration (min)				.055	<.001
Pre	8.2 (2.6)	7.2 (2.5)	7.3 (2.1)		
Post	9.1 (2.9)	6.9 (2.5)	7.0 (1.9)		
Peak HR (bpm)				.385	<.001
Pre	140 (21)	133 (22)	133 (20)		
Post	143 (21)	127 (21)	128 (22)		
Peak RER				.717	.373
Pre	1.12 (0.1)	1.09 (0.1)	1.11 (0.09)		
Post	1.11 (0.1)	1.08 (0.11)	1.09 (0.11)		

Note: P-values for planned contrasts are from adjusted models controlling for age, gender, race, history of myocardial infarction, baseline HADS-A, presence of an anxiety disorder, and the baseline level of the outcome, with treatment group as the predictor of interest.

Values represent mean (standard deviation) for each parameter.

V0$_2$ = Aerobic capacity; HR = heart rate; RER = Respiratory Exchange Ratio (CO$_2$ production/O$_2$ uptake).

Participants in the exercise group were prescribed 3 exercise sessions per week for 12 weeks; 41 (79%) participants attended at least 80% of sessions.

eTable 2. Weekly Spielberger State-Trait Anxiety Inventory-State scores by treatment group

Week	1	2	3	4	5	6	7	8	9	10	11	12
Exercise mean (SD)	33.6 (9.6)	34.1 (9.8)	33.8 (9.8)	36 (11.9)	33.3 (9.3)	33.6 (9.8)	32.8 (8.8)	31.9 (10.6)	33.8 (10.1)	32.8 (9.9)	31.1 (10.2)	30.4 (8.7)
Escitalopram Mean (SD)	34.3 (9.3)	32 (8.9)	31.9 (9.3(	31.9 (9.4)	30.2 (9.0)	30.1 (8.6)	29.9 (8.7)	31.3 (11.9)	30.1 (9.0)	29.2 (8.7)	30.6 (9.3)	30.4 (9.5)
Placebo Mean (SD)	35.2 (6.7))	34.7 (11.0))	34.7 (8.4)	33.8 (7.6)	37.3 (11.2)	32.3 (8.1)	35.6 (10.4)	33.8 (9.4)	34.2 (9.8)	31 (7.5)	31.9 (10.3)	33.5 (9.1)

eTable 3. Pretreatment and posttreatment levels of supplementary anxiety measures

Instrument	Aerobic Exercise	Escitalopram	Placebo	Contrast 1: exercise / escitalopram vs placebo	Contrast 2: exercise vs escitalopram
HAM-A				.554	.036
PRE-	15.2 (5.9)	15.8 (6.3)	17.7 (7.5)		
POST-	10.8 (5.2)	8.9 (5.4)	9.8 (5.0)		
				.229	.042
STAI-T					
PRE-	42.1 (7.6)	41.4 (6.5)	43.0 (7.6)		
POST-	37.1 (7.3)	34.7 (5.8)	37.7 (6.5)		
GAD-7				.770	.022
PRE-	7.7 (4.0)	6.6 (4.5)	7.7 (4.7)		
POST-	3.7 (3.2)	2.3 (3.0)	2.8 (2.4)		
ASI				.167	.129
PRE-	23.1 (12.1)	21.7 (12.1)	27.5 (13.2)		
POST-	17.4 (11.2)	14.5 (8.1)	20.5 (11.5		

 Note: P-values for planned contrasts are from adjusted models controlling for age, gender, race, history of myocardial infarction, presence of an anxiety disorder, and the baseline level of the outcome, with treatment group as the predictor of interest. Values represent mean (standard deviation); HAM-A = Hamilton Rating Scale for Anxiety; STAI-T = Spielberger State-Trait Anxiety Inventory-Trait; GAD-7 = Generalized Anxiety Disorder Scale-7 items; ASI = Anxiety Sensitivity Index

eTable 4. Pretreatment and posttreatment depression scores (mean and sd) for the Beck Depression Inventory-II and Hospital Anxiety and Depression-Depression Subscale

Instrument	AEROBIC EXERCISE	ESCITALOPRAM	PLACEBO	Contrast 1: exercise / escitalopram vs placebo	Contrast 2: exercise vs escitalopram
BDI-II				.284	.026
PRE	16.2 (8.0)	15.2 (7.7)	17.7 (7.9)		
POST	8.8 (6.5)	6.0 (5.2)	9.0 (5.5)		
HADS-D				.348	.023
PRE	6.4 (3.0)	6.7 (2.7)	7.0 (2.9)		
POST	4.1 (2.7)	3.2 (2.7)	4.3 (2.7)		

Note: Values are presented as mean (SD). P-values for planned contrasts are from adjusted models controlling for age, gender, race, history of myocardial infarction, presence of an anxiety disorder, and the baseline level of the outcome, with treatment group as the predictor of interest.

BDI-II = Beck Depression Inventory II; HADS-D = Hospital Anxiety and Depression Scale-Depression subscale

eTable 5. Pretreatment and posttreatment levels of coronary heart disease biomarkers and sympathetic nervous system activity

Variable	Aerobic Exercise	Escitalopram	Placebo	Contrast 1: exercise / escitalopram vs placebo	Contrast 2: exercise vs escitalopram
Heart Rate Variability and Baroreflex Sensitivity					
SDNN,(ms)				.595	.504
PRE	140 (81)	155 (124)	164 (88)		
POST	138 (88)	146 (132)	169 (110)		
BRS (ms/mm Hg)				.640	.294
PRE	5.4 (2.7)	4.9 (3.4)	7.5 (2.8)		
POST	5.1 (2.6)	5.3 (3.4)	7.1 (5.1)		
Endothelial Function					
Flow Mediated Dilation, (%)				.877	.717
PRE	3.0 (2.7)	2.6 (2.0)	2.8 (3.2)		
POST	3.5 (3.6)	3.2 (2.8)	3.0 (2.5)		

Sympathetic Nervous System Activity					
Epinephrine (ng/mg)				.131	.038
PRE	4.4 (2)	5.1 (3)	3.6 (2)		
POST	4.4 (3)	3.4 (2)	4.4 (2)		
Norepinephrine (ng/mg)				.012	.107
PRE	37.4 (11)	40.1 (21)	39.8 (12)		
POST	35.9 (12)	33.2 (15)	40.5 (10)		

Note: Values are presented as mean (SD). P-values for planned contrasts are from adjusted models controlling for age, gender, race, history of myocardial infarction, presence of an anxiety disorder, baseline HADS-A, and the baseline level of the outcome, with treatment group as the predictor of interest. Analysis of flow mediated dilation (FMD) is also adjusted for baseline arterial diameter.