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CME

Exercise and Pharmacological Treatment of Depressive Symptoms in Patients With Coronary Heart Disease

Results From the UPBEAT (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) Study

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CME Objective for This Article: At the conclusion of this activity, the learner should be able to assess the efficacy of exercise and antidepressant medication in reducing depressive symptoms and improving cardiovascular biomarkers in depressed patients with coronary heart disease.

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Exercise and Pharmacological Treatment of Depressive Symptoms in Patients With Coronary Heart Disease

Results From the UPBEAT (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) Study

Objectives The aim of this study was to assess the efficacy of exercise and antidepressant medication in reducing depressive symptoms and improving cardiovascular biomarkers in depressed patients with coronary heart disease.

Background Although there is good evidence that clinical depression is associated with poor prognosis, optimal therapeutic strategies are currently not well defined.

Methods One hundred one outpatients with coronary heart disease and elevated depressive symptoms underwent assessment of depression, including a psychiatric interview and the Hamilton Rating Scale for Depression. Participants were randomized to 4 months of aerobic exercise (3 times/week), sertraline (50–200 mg/day), or placebo. Additional assessments of cardiovascular biomarkers included measures of heart rate variability, endothelial function, baroreflex sensitivity, inflammation, and platelet function.

Results After 16 weeks, all groups showed improvement on Hamilton Rating Scale for Depression scores. Participants in both the aerobic exercise (mean −7.5; 95% confidence interval: −9.8 to −5.0) and sertraline (mean −6.1; 95% confidence interval: −8.4 to −3.9) groups achieved larger reductions in depressive symptoms compared with those receiving placebo (mean −4.5; 95% confidence interval: −7.6 to −1.5; $p = 0.034$); exercise and sertraline were equally effective at reducing depressive symptoms ($p = 0.607$). Exercise and medication tended to result in greater improvements in heart rate variability compared with placebo ($p = 0.052$); exercise tended to result in greater improvements in heart rate variability compared with sertraline ($p = 0.093$).

Conclusions Both exercise and sertraline resulted in greater reductions in depressive symptoms compared to placebo in patients with coronary heart disease. Evidence that active treatments may also improve cardiovascular biomarkers suggests that they may have a beneficial effect on clinical outcomes as well as on quality of life. (Exercise to Treat Depression in Individuals With Coronary Heart Disease; NCT00302068) (J Am Coll Cardiol 2012;60: 1053–63) © 2012 by the American College of Cardiology Foundation

The term "cardiovascular vulnerable patients" has been used to describe patients susceptible to acute coronary events on the basis of plaque, blood markers, or myocardial characteristics (1). There now is growing evidence that psychological depression is associated with increased vulnerability, as it is a significant and independent risk factor for adverse outcomes in patients with coronary heart disease (CHD) (2–4).

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Clinical depression is relatively common in patients with CHD, with estimates of 15% to 20% of cardiac patients meeting criteria for major depressive disorder (MDD) and an additional 20% reporting elevated depressive symptoms (5–7). A number of studies have reported that the presence of clinical depression is associated with more than a doubling of risk for mortality and nonfatal cardiac events (8,9) and that even subclinical elevations in depressive symptoms are associated with a worse prognosis in patients with established CHD (6,7).

The high prevalence of elevated depressive symptoms in CHD populations and the increased risk for untoward cardiac events associated with depression led the American Heart Association to issue an advisory statement recommending that patients with CHD should be screened for depressive symptoms (4). However, the value of screening patients for depression has been controversial (10,11), in part because of a paucity of evidence supporting the value of treating depression in cardiac patients. Although antidepressant medication is widely considered to be the treatment of choice (12), for a number of patients, medication fails to adequately relieve depressive symptoms or does so at the cost of unwanted side effects (13). Moreover, there have been few randomized clinical trials of established treatments for depression in cardiac patients, and results have been negative or equivocal (14–18).

There is now good reason to believe that exercise may be a viable alternative to traditional mental health interventions in cardiac patients. An increasing number of studies have shown that exercise may reduce depressive symptoms in patients with MDD (19) and that exercise may be comparable with established psychological (20) or pharmacological (21,22) therapies. However, to our knowledge, no randomized clinical trial has examined the effects of exercise on depression in patients with CHD. Because depression also is related to biomarkers of cardiovascular risk, including reduced heart rate variability (HRV) (23), low baroreflex sensitivity (BRS) (24), impaired vascular endothelial func-

tion (25), increased platelet activation, and heightened inflammation (26), as well as health behaviors such as physical inactivity (27), a secondary goal of the study was to examine the effects of exercise and antidepressant medication on these key cardiovascular biomarkers.

Methods

Trial overview. The aims of the UPBEAT (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) study were to: 1) evaluate the effectiveness of exercise training in reducing depression in patients with CHD; and 2) examine changes in physiologic biomarkers of cardiac vulnerability, including measures of HRV, BRS, vascular endothelial function, inflammation, and platelet aggregation. Enrollment began in June 2006 and ended in September 2010. Participants were recruited from physician referrals, community-based screenings, and mass media advertisements. After the completion of baseline assessments (see the following discussion), participants were randomized to exercise, sertraline, or a placebo pill. At the conclusion of the 4-month treatment period, assessments were repeated.

UPBEAT was an investigator-initiated trial sponsored by the National Heart, Lung, and Blood Institute. Sertraline (Zoloft) and matching placebo pills were supplied by Pfizer, Inc. (New York, New York), which had no role in the oversight or design of the study or in the analysis or interpretation of the data. The trial was approved by the institutional review board at Duke University Medical Center, and written informed consent was obtained from all participants. An independent data and safety monitoring board oversaw the conduct of the study and reviewed the safety and efficacy data.

Participants. Eligibility criteria included age 35 years or older, documented CHD (e.g., prior myocardial infarction, revascularization procedure, or significant [>70% stenosis] coronary atherosclerosis), and elevated score (≥7) on the Beck Depression Inventory (28). Exclusion criteria included the presence of another primary psychiatric diagnosis, such as a history of bipolar disorder or psychosis; medical comorbidities that would preclude participation in the trial (e.g., significant musculoskeletal disease, cancer); current psychotherapy or use of antidepressants or other psychotropic medications; history of inability to tolerate or benefit from sertraline; use of dietary supplements or herbal therapies with purported psychoactive indications; current active alcohol or drug abuse or dependence; active suicidal intent; and participation in regular exercise >1 day/week.

Assessment procedures. MEDICAL SCREENING. Before entry into the study, patients underwent physical examinations by study physicians. Blood pressure was measured using standard sphygmomanometry in sitting and standing positions. Blood specimens were acquired after an overnight fast for routine electrolytes, pregnancy and liver function tests, blood count, and thyroid-stimulating hormone assessment. If a patient was found to have any significant medical condition that would contraindicate safe participation in the study, he or she was excluded from participation.

Abbreviations and Acronyms

βTG = beta-thromboglobulin
BRS = baroreflex sensitivity
CHD = coronary heart disease
CI = confidence interval
FMD = flow-mediated dilation
HAM-D = Hamilton Depression Rating Scale
HRV = heart rate variability
MDD = major depressive disorder
PF4 = platelet factor 4
SDNN = standard deviation of the normal-to-normal R-R intervals

DEPRESSION ASSESSMENT. All potential participants were evaluated using the Structured Clinical Interview for Depression (29) to determine the presence of MDD and the 17-item Hamilton Depression Rating Scale (HAM-D) (30) to assess the severity of depressive symptoms, both at baseline and after 4 months. Assessments were performed by clinical psychologists blinded to treatment condition. To ensure patient safety, psychologists blinded to the treatment group administered the HAM-D by telephone weekly for the first 4 weeks and biweekly for the subsequent 12 weeks to monitor symptom severity and presence of suicidality.

EXERCISE TESTING. 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 in which work loads were increased at a rate of 1 metabolic equivalent/min (31). Expired gases were analyzed continuously using a Parvo Medics True One measurement system (Parvo Medics, Sandy, Utah).

HEART RATE VARIABILITY. For our primary cardiovascular biomarker, an electrocardiogram was recorded for 24 h using the Lifecard CF, a 3-channel digital compact flash Holter recorder (DelMar Reynolds, Irvine, California). During the recording period, patients engaged in their normal patterns of activity. Electrocardiographic data were downloaded and edited using the Pathfinder digital ambulatory electrocardiographic analyzer (DelMar Reynolds), and HRV was estimated from the standard deviation of the normal-to-normal R-R intervals (SDNN).

ENDOTHELIAL FUNCTION ASSESSED BY FLOW-MEDIATED DILATION (FMD). Brachial artery FMD was assessed after overnight fasting (32). Longitudinal B-mode ultrasound images of the brachial artery, 4 to 6 cm proximal to the antecubital crease, 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 after the inflation of a forearm pneumatic occlusion cuff to suprasystolic pressure (about 200 mm Hg) for

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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.

BAROREFLEX SENSITIVITY. Beat-by-beat systolic blood pressure and heart rate were collected using the Finapres noninvasive blood pressure monitor (model 2300; Ohmeda, Madison, WI). Recordings of beat-by-beat blood pressure and R-R interval (derived as 60,000/heart rate) were edited for artifacts, linearly interpolated, and resampled at a frequency of 4 Hz, to generate an equally spaced time series. A fast Fourier transformation was then applied to the interpolated data after detrending and the application of a Hanning filtering window. BRS was estimated from the magnitude of the transfer function relating R-R interval oscillations to systolic blood pressure oscillations across the low-frequency band (0.07–0.1299 Hz).

INFLAMMATION AND PLATELET FUNCTION. Plasma inflammatory markers were measured using enzyme-linked immunosorbent assay. Platelet factor 4 (PF4) and beta-thromboglobulin (βTG) were measured using enzyme-linked immunosorbent assay using commercially available kits manufactured by American Diagnostica (Stamford, Connecticut) and Diagnostica Stago (Parsippany, New Jersey), respectively.

Treatment. Participants were randomly assigned to exercise, sertraline, or placebo in a pre-determined 2:2:1 ratio. Randomization was performed centrally by computer with conditional randomization (stratified by age [35 to 59 vs. ≥60 years], CHD status [prior myocardial infarction vs. no myocardial infarction], and depression severity [HAM-D score >18 vs. ≤18]); patients were provided with sealed envelopes containing their group assignments.

AEROBIC EXERCISE. Patients in the exercise condition attended 3 supervised group aerobic exercise sessions per week for 16 weeks. On the basis of peak heart rate achieved during the initial treadmill test, patients were assigned training ranges equivalent to 70% to 85% maximal heart rate reserve. Each aerobic session consisted of 30 min of walking or jogging on a treadmill at an intensity that would maintain heart rate within the assigned training range.

SERTRALINE OR PLACEBO PILL. Participants in the 2 pill conditions were given the selective serotonin reuptake inhibitor sertraline or a matching placebo. Medications were taken once daily; the dosage depended on the clinical response, but usually, each patient started at 50 mg (1 pill) of drug or placebo and progressed up to 200 mg (4 pills), contingent on therapeutic response and the presence of side effects. The treating psychiatrist was blinded to pill condition and used supportive measures to help manage medication side effects.

Outcome assessors were unaware of patients' treatment assignments, and only the research pharmacist was aware of which patients were assigned to sertraline or to placebo.

The primary endpoint was the HAM-D score at the end of 4 months. Secondary endpoints included remission of depression, defined as no Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, diagnosis of MDD (33) and a HAM-D score <8 (34), and cardiovascular biomarkers.

Statistical analysis. The effect of treatment on the primary and secondary outcomes was evaluated using the general linear model for continuous variables and unadjusted chi-square tests for the categorical depression diagnoses and side-effect outcomes, using SAS version 9.1 (SAS Institute Inc., Cary, North Carolina). Separate models were estimated for each outcome, with the following predictors: a treatment group indicator variable, the corresponding pre-treatment value of the outcome, age, sex, and ethnicity (Caucasian vs. non-Caucasian). For the HAM-D outcome, we tested 2 orthogonal contrasts: 1) active treatments (i.e., exercise and sertraline) versus placebo and 2) exercise versus sertraline. In cases in which model residuals did not meet assumptions, we transformed the outcome and corresponding baseline level of the outcome to ranks, again using the general linear model. This occurred for SDNN, BRS, C-reactive protein, interleukin-6, βTG, and PF4. This approach reduces potential bias due to outlying values, allows the data to better meet model assumptions with respect to the distribution of residuals, and has been shown to be equivalent to conventional nonparametric tests (35). Unless otherwise indicated, treatment effects were analyzed following the intent-to-treat principle, with post-treatment missing data managed using the multiple imputation method available in SAS PROC MI. We estimated that our sample size would yield about 80% power to detect a 0.66 standard deviation difference between the active treatments and placebo control and a 0.65 standard deviation difference between the two active treatments.

Results

Participant flow. Figure 1 displays the flow of participants through the course of the study. Of the 1,680 participants who initially inquired about the study, 284 met our initial inclusion criteria. After screening, 101 participants were randomized: 37 to the exercise condition, 40 to sertraline, and 24 to placebo.

Participant characteristics. The sample was generally middle-aged and older (mean age 63.9 years), primarily white (73%), and primarily male (68%). The majority of participants were married, were relatively affluent, and had at least some college education (Table 1). Forty-seven participants (47%) met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria for MDD at baseline: 46% (n = 17) in the exercise group, 50% (n = 20) in the sertraline group, and 42% (n = 10) in the placebo group.

Adherence to exercise and medication. Of the 48 expected exercise sessions, the median number attended was 45 (94%). Pill adherence was defined as the number of pills taken divided by the number prescribed. The median

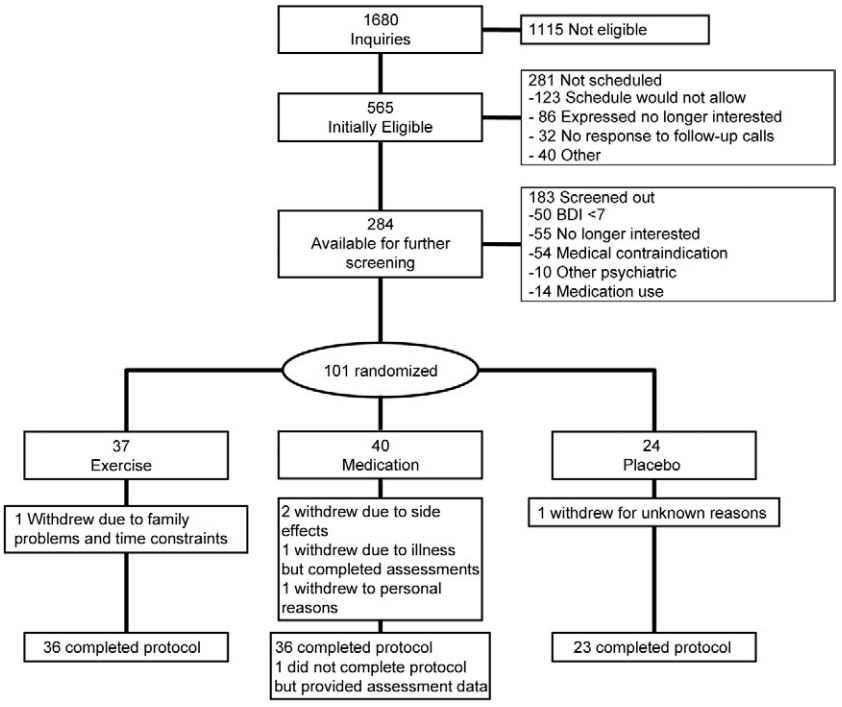

Figure 1 **Participant Flow in the UPBEAT Randomized Clinical Trial**

BDI = Beck Depression Inventory; UPBEAT = Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy.

adherence to the pill conditions was 100% (interquartile range: 97% to 101%), ranging from 83% to 112%. The median sertraline dose was 50 mg (interquartile range: 50 to 100 mg).

Side effects. Untoward effects of each treatment were examined by patient ratings on a 36-item symptom checklist, which was obtained before and after treatment (e.g., headaches, dizziness, constipation, muscle pain and soreness). Symptoms were rated on a 5-point, Likert-type scale ranging from 0 ("never") to 4 ("almost always"). Relatively few patients reported a worsening of symptoms after treatment. Among the 36 side effects assessed, only 2 showed a significant group difference: 20% of patients receiving sertraline reported worse post-treatment fatigue compared with 2.4% in the exercise group and 8.8% in the placebo group ($p = 0.025$), and 26% reported increased sexual problems compared with 2.4% in the exercise group and 11.8% in the placebo group ($p = 0.005$).

Changes in aerobic fitness. The exercise group exhibited greater improvements in peak oxygen consumption and exercise endurance compared with the sertraline and placebo groups. Adjusting for pretreatment levels, age, sex, and ethnicity, the mean post-treatment peak oxygen consumption was greater with exercise (21.3 ml/kg/min; 95% confidence interval [CI]: 20.3 to 22.3 ml/kg/min) compared with sertraline (18.5 ml/kg/min; 95% CI: 17.5–19.4 ml/kg/min; $p < 0.001$) and placebo (18.5 ml/kg/min; 95% CI: 17.2–19.8 ml/kg/min; $p = 0.002$) (Fig. 2A). Participants in the exercise group showed a 9.6% increase in peak oxygen consumption compared with sertraline (2.3%) and placebo (2.1%). Similarly, at 16 weeks, treadmill test duration was longer in the exercise group (8.8 min; 95% CI: 8.3 to 9.4 min) compared with the sertraline (7.1 min; 95% CI: 6.6 to 7.7 min; $p < 0.001$) and placebo (7.2 min; 95% CI: 6.5 to 8.0; $p < 0.001$) groups (Fig. 2B). The values represented a 19% increase from baseline for exercise and 0.5% and 1% decreases for sertraline and placebo, respectively. Body weight remained essentially constant throughout the study; there were no group differences in post-treatment body mass index.

Changes in depression. After 16 weeks, all groups showed improvements in HAM-D scores. The raw changes in scores from baseline to 16 weeks among participants with complete data were as follows: exercise, −7.5 (95% CI: −9.8 to −5.0); sertraline, −6.1 (95% CI: −8.4 to −3.9); and placebo, −4.5 (95% CI: −7.6 to −1.5). The combined active treatments showed lower HAM-D scores at 16 weeks compared with placebo ($p = 0.034$), and there was no difference between exercise and sertraline ($p = 0.607$) (Fig. 3). On the basis of the intention-to-treat analysis, the HAM-D scores after 16 weeks in the exercise group were 3.3 points lower compared with the placebo group, while the average score in the sertraline group was 1.7 points lower compared with the placebo group.

Among patients diagnosed with MDD initially who were available for follow-up ($n = 44$), we examined rates of

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Table 1 Background Characteristics of Sample

Variable	Exercise (n = 37)	Sertraline (n = 40)	Placebo (n = 24)	p Value*
Age (yrs)	64.7 ± 11.0	63.4 ± 10.2	63.5 ± 11.4	0.911
Men	65% (24)	63% (25)	83% (20)	0.189
Ethnicity				0.403
Caucasian	81% (30)	70% (28)	67% (16)	
African American	8% (3)	23% (9)	13% (3)	
Hispanic	3% (1)	0	4% (1)	
Asian/Pacific Islander	5% (2)	3% (1)	8% (2)	
Native American	0	3% (1)	8% (2)	
Other	3% (1)	3% (1)	0	
Level of education				
Less than high school	8% (3)	8% (3)	0	0.792
High School	11% (4)	28% (11)	21% (5)	
Some college	14% (5)	28% (11)	29% (7)	
Completed college	11% (4)	15% (6)	8% (2)	
Some post-graduate	16% (6)	13% (5)	13% (3)	
Complete post-graduate	11% (4)	5% (2)	25% (6)	
Annual household income				0.276
<$45,000	43% (16)	53% (21)	33% (8)	
$45,000–$49,999	19% (7)	15% (6)	13% (3)	
$50,000–$75,000	14% (5)	3% (1)	13% (3)	
>$75,000	22% (8)	25% (10)	33% (8)	
Married	73% (27)	70% (28)	67% (16)	0.869
Employed full-time	32% (12)	25% (10)	38% (9)	0.553
Medications				
Beta-blockers	92% (34)	83% (33)	96% (23)	0.201
ACE inhibitors or ARBs	51% (19)	60% (24)	75% (18)	0.182
Aspirin	92% (34)	83% (33)	96% (23)	0.201
Other antiplatelet agents	49% (18)	53% (21)	58% (14)	0.761
Cholesterol-lowering medications	86% (32)	78% (31)	79% (19)	0.567
Nitrates	22% (8)	40% (16)	29% (7)	0.214
Prior MI	35% (13)	28% (11)	25% (6)	0.647
Prior percutaneous revascularization	68% (25)	51% (20)	75% (18)	0.097
Prior CABG	22% (8)	33% (13)	29% (7)	0.558
Total cholesterol (mg/dl)	152.8 ± 35.1	165.8 ± 49.0	158.6 ± 27.9	0.602
LDL cholesterol (mg/dl)	83.5 ± 30.5	92.9 ± 39.7	82.1 ± 15.1	0.743
HDL cholesterol (mg/dl)	44.0 ± 11.3	42.6 ± 10.1	46.6 ± 12.8	0.620
Serum triglycerides (mg/dl)	126.4 ± 62.5	144.2 ± 80.9	157.0 ± 140.0	0.559
Baseline HAM-D score	13.4 ± 5.9	14.3 ± 5.8	14.5 ± 5.8	0.764
BDI score at baseline	18.5 ± 7.0	17.7 ± 9.3	17.5 ± 9.5	0.550
DSM diagnosis of major depression	46% (17)	50% (20)	42% (10)	0.549
Systolic blood pressure (mm Hg)	130 ± 22	132 ± 20	126 ± 14	0.604
Diastolic blood pressure (mm Hg)	80 ± 11	72 ± 11	71 ± 10	0.670
Peak Vo_2 (ml/kg/min)	19.5 ± 4.8	18.5 ± 6.0	20.1 ± 7.4	0.564
Body mass index (kg/m^2)	31.0 ± 5.7	31.5 ± 4.4	30.8 ± 5.1	0.947

Values are mean ± SD or % (n). *p values provided at the journal's request are based on Pearson chi-square tests for categorical variables and Kruskal-Wallis or general linear model tests for continuous variables.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BDI = Beck Depression Inventory; CABG = coronary artery bypass grafting; *DSM* = *Diagnostic and Statistical Manual of Mental Disorders*; HAM-D = Hamilton Depression Rating Scale; HDL = high-density lipoprotein; IL = interleukin; LDL = low-density lipoprotein; MI = myocardial infarction; Vo_2 = oxygen consumption.

remission at 16 weeks, defining remission as the absence of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria for MDD and a HAM-D score <8 (34). Among the exercise group, 40% (6 of 15) were remitted, compared with 10% (2 of 20) in the sertraline group and no participants (0 of 9) in the placebo group (chi-square = 7.70, 2 degrees of freedom, p = 0.021). Among participants who did not meet the criteria for MDD at baseline, 1 participant in the exercise group and 1 participant in the placebo group met MDD criteria at 16 weeks. We also examined HAM-D scores among the same subgroup of patients initially diagnosed with MDD. Again, the contrast for active treatments versus placebo was significant (p = 0.042), while the contrast between exercise and

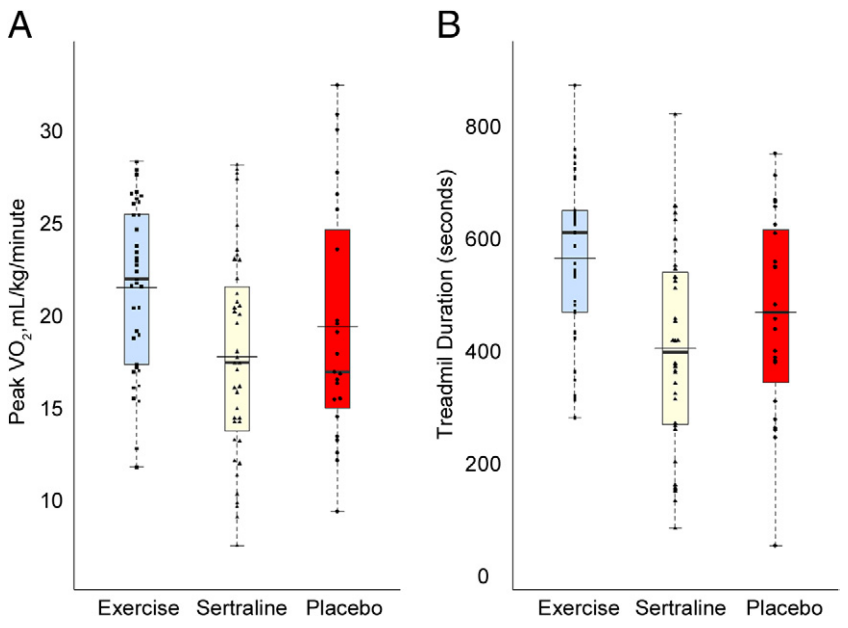

Figure 2 **Aerobic Capacity and Treadmill Time at 16 Weeks Adjusted for Age, Sex, Ethnicity, and Baseline Scores of the Outcome**

(A) Aerobic capacity; **(B)** treadmill time. Contrasts were planned and nonorthogonal: exercise versus sertraline and exercise versus placebo, with Bonferroni correction. The **thicker horizontal line** represents the median, and the **thinner, wider line** represents the mean. **Boxes** represent 25th and 75th percentiles. After treatment, exercise was associated with higher levels of aerobic capacity and longer treadmill time compared with either sertraline or placebo ($p < 0.001$). VO_2 = oxygen consumption.

sertraline was not ($p = 0.579$). The mean adjusted HAM-D scores at 16 weeks were 8.8 (95% CI: 6.1 to 11.6) for exercise, 9.9 (95% CI: 7.4 to 12.3) for sertraline, and 13.6 (95% CI: 10.0 to 17.2) for placebo. Among this subgroup, the changes in HAM-D scores from baseline to 16 weeks were −9.4 (95% CI: −12.4 to −6.4) for exercise, −8.6

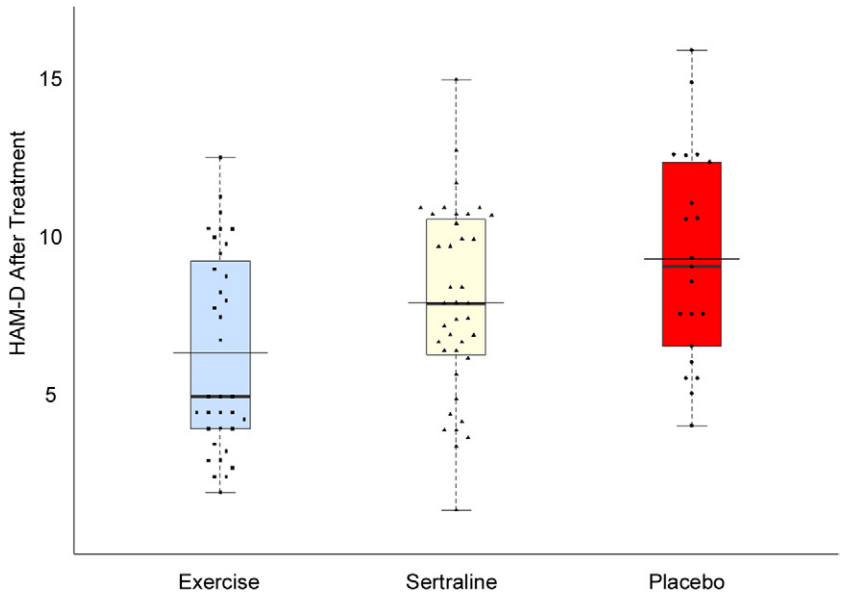

Figure 3 **HAM-D Scores Adjusted for Age, Sex, Ethnicity, and Baseline Scores of the Outcome**

The **thicker horizontal line** represents the median, and the **thinner, wider line** represents the mean. **Boxes** represent 25th and 75th percentiles. Hamilton Depression Rating Scale (HAM-D) scores were lower for the active treatments (exercise and sertraline) compared with placebo ($p = 0.034$) but were not different from each other ($p = 0.607$).

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Table 2 Biomarkers Before and After Treatment

Biomarker Variable	Exercise Only	Sertraline	Placebo	Contrast p Value: All Active Treatment vs. Placebo	Contrast p Value: Exercise vs. Sertraline
SDNN (ms)*					
Before	116	120	123		
After	122	118	112	0.052	0.093
Change	+6	−2	−11		
BRS (ms/mm Hg)†					
Before	4.8	4.7	4.9		
After	4.0	5.1	4.1	0.515	0.046
Change	−0.8	+0.4	−0.7		
FMD (%)					
Before	3.5	2.6	4.4		
After	3.0	4.1	3.3	0.727	0.131
Change	−0.5	+1.5	−1.1		
CRP (μg/ml)					
Before	2.5	2.5	2.4		
After	2.1	2.5	2.5	0.567	0.343
Change	−0.4	0	+0.1		
IL-6 (pg/ml)					
Before	1.98	1.7	1.95		
After	1.80	2.1	1.85	0.828	0.040
Change	−0.10	+0.4	−0.10		
PF4 (IU/ml)					
Before	44.1	34.1	32.0		
After	35.5	34.0	34.4	0.995	0.712
Change	−8.6	−0.1	+2.4		
βTG					
Before	137.0	102.5	103.1		
After	134.3	129.0	125.0	0.830	0.968
Change	−2.7	+16.5	+22.1		

Values in rows labeled "before" are pre-treatment means. Values in rows labeled "after" are adjusted post-treatment means. With the exception of FMD, analyses were performed on imputed rank-transformed values, adjusted for baseline level of corresponding outcome, age, sex, and race. Pre-treatment and post-treatment means in the table were estimated from the ranks, using the nearest value in the original metric that corresponded to the rank. Pre-treatment values are based on the raw ranks, while post-treatment means were estimated from the adjusted post-treatment ranks. Analysis of treatment effect on FMD was performed on imputed values in original metric, adjusted for baseline level of FMD, baseline arterial diameter, age, sex, and race. *Analysis based on 93 participants with valid baseline measurements. †Analysis based on 92 participants with valid baseline measurements.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BDI = Beck Depression Inventory; CABG = coronary artery bypass grafting; *DSM* = *Diagnostic and Statistical Manual of Mental Disorders*; HAM-D = Hamilton Depression Rating Scale; HDL = high-density lipoprotein; IL = interleukin; LDL = low-density lipoprotein; MI = myocardial infarction; Vo_2 = oxygen consumption.

(95% CI: −11.1 to −6.1) for sertraline, and −4.5 (95% CI: −8.4 to −0.7) for placebo.

Biomarker endpoints. All biomarker endpoint data are reported in Table 2. For SDNN, our measure of HRV, the contrast between the active treatments and placebo approached significance (p = 0.052). At the conclusion of treatment, the exercise group displayed higher 24-h SDNN compared with the placebo group. For BRS, the active treatments combined were not different from placebo (p = 0.515), but exercise was lower compared with sertraline (p = 0.046). For inflammatory biomarkers, patients randomized to exercise had lower levels of interleukin-6 after treatment compared with those treated with sertraline (p = 0.040), but the active treatments combined were not different from placebo (p = 0.828). There were no treatment group differences for FMD, C-reactive protein, βTG, or PF4.

Discussion

The results of the UPBEAT trial confirm and extend evidence for the value of aerobic exercise to treat depression. Participants with CHD and elevated depressive symptoms who were prescribed aerobic exercise 3 times per week for 30 to 45 min per session achieved significantly greater reductions in depressive symptoms compared with placebo controls; the reduction in depressive symptoms associated with exercise was comparable with that observed in patients receiving antidepressant medication. Furthermore, exercise was even more effective in reducing clinical depression in the subset of patients who were diagnosed with MDD at study entry. Although the sample was small, 40% of patients with MDD at the time of randomization were remitted at the end of 16 weeks of exercise, compared with 10% of those who received sertraline and none of the patients who

received placebo. These data add to the growing body of research suggesting that exercise may be a viable alternative to traditional psychopharmacological treatments of depression.

In an initial study from our group, exercise was shown to be as effective as antidepressant medication in noncardiac patients with MDD (21). Because there was no control condition, however, the benefits could not be attributed to exercise. In a subsequent study (22), both group exercise and home-based exercise proved comparable with antidepressant medication and were superior to placebo controls in non-CHD patients diagnosed with MDD. The present findings extend these prior reports by demonstrating that exercise reduces depressive symptoms in patients with stable CHD. These results may be particularly important in light of the growing evidence that depression is associated with increased risk for fatal and nonfatal events in a wide range of CHD populations (3,4,7,9).

To date, there is limited evidence that traditional treatments are effective for depressed patients with CHD. The Sertraline Antidepressant Heart Attack Trial reported that sertraline was no better than placebo in reducing depression in the entire sample of patients with acute coronary syndromes but was more effective compared with placebo in reducing depressive symptoms in the subgroup of patients with more severe MDD (14). The subsequent SADHART-CHF (Sertraline Against Depression and Heart Disease in Chronic Heart Failure) trial showed that sertraline performed no better than placebo in patients with heart failure after 12 weeks of treatment and did not improve clinical outcomes (15). The CREATE (Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy) trial showed that citalopram was associated with greater reductions in depressive symptoms compared with placebo in patients with CHD, but participants also received concomitant counseling from nurse clinicians, and such counseling was found to be more effective than interpersonal psychotherapy (16). In the ENRICHD (Enhancing Recovery in Coronary Heart Disease Patients) trial (18), post–myocardial infarction patients who received cognitive behavior therapy exhibited greater reductions in HAM-D scores compared with health education controls, although there were no treatment group differences in clinical outcomes. Interestingly, secondary analyses of that trial found that exercise (36) and antidepressant medications (37) were associated with reduced mortality and nonfatal myocardial infarction. However, because the patients were not randomly assigned to exercise or medication, it was unclear whether either treatment was responsible for the observed effects. Milani et al. (38) reported that exercise reduced depression in patients with CHD, but because participants received concurrent treatments and were not randomized, reduced depressive symptoms could not be attributed to exercise. To our knowledge, UPBEAT is the first randomized clinical trial to show that exercise improves depression in patients with CHD with MDD or subclinical depressive symptoms.

In addition to reduced depression, the 2 active treatments, especially exercise, resulted in increased HRV in study participants compared with placebo controls. These findings are consistent with studies of exercise training in healthy adults (39) and in patients with CHD (40). Prior studies evaluating antidepressant medications have found either no effect or possible unfavorable effects on HRV (14,41).

No improvements were observed in BRS in the treatment groups compared with placebo controls, although sertraline resulted in improved BRS compared with exercise. We also found no evidence for improvements in measures of chronic inflammation in the active treatments compared with placebo, although exercise resulted in greater improvements in interleukin-6 compared with sertraline. Previously, we found that vascular endothelial function was improved by exercise (42), but no such benefit was observed in the present study. In the Sertraline Antidepressant Heart Attack Trial, depressed patients with CHD treated with sertraline had lower levels of βTG compared with those treated with placebo, although there was no difference in PF4. We found no effect of drug therapy on either of these markers of platelet activation.

Although there were few side effects associated with treatment, sertraline was associated with more fatigue and greater sexual dysfunction relative to placebo and exercise. Sexual dysfunction is a common symptom of depression (43) and may be a common side effect of selective serotonin reuptake inhibitors (44), while aerobic exercise has been associated with improved sexual function among men with erectile dysfunction (45) and with better overall sexual function compared with sertraline or placebo pill (46).

Study limitations. Our relatively small sample size likely limited our ability to detect small treatment effects for the biomarkers. Several issues may affect the generalizability of our findings. The extent to which UPBEAT patient volunteers are representative of the general population of depressed patients with CHD is uncertain. Participants had to be willing to accept the condition to which they were randomly assigned, and patients who were not interested in exercise or taking an antidepressant were unlikely to have volunteered. We also note that our sample was highly educated, with three-quarters of the sample attending at least some college, which may help explain the high adherence rates observed in our trial.

Another limitation is that we did not examine the optimal dose of exercise necessary to improve depression. All patients received an exercise prescription of approximately 90 min of exercise per week (i.e., 30 min 3 times/week). Patients were also on relatively low doses of sertraline, with only 30% of patients receiving >100 mg of sertraline by the end of the trial. Higher doses may have produced more favorable effects on the biomarkers but were difficult to justify in participants who did not meet criteria for MDD. Because exercise training was supervised group exercise, it was confounded with social support, which may

have augmented the beneficial effects of exercise. However, our previous work showed that unsupervised, home-based exercise produced similar reductions in depressive symptoms compared with supervised exercise (22), and the Depression Outcomes Study of Exercise established that exercise was effective in improving depression independent of social support (47).

Conclusions

The present findings from UPBEAT indicate that depression can be reduced in cardiac patients. Because of the paucity of evidence that depression can be successfully treated, some have questioned the merits of assessing depression in patients with CHD (10). We believe that the evidence documenting the association of depression with poor prognosis and the present findings that depressive symptoms can be reduced support the recommendation that routine monitoring of depressive symptoms in patients with CHD should be performed. Although improvements in biomarkers do not necessarily translate into improved clinical outcomes (48), our finding that HRV may be reduced in depressed cardiac patients is encouraging. Although further research with larger samples is warranted, these findings provide preliminary evidence that cardiac patients with elevated depressive symptoms are likely to benefit from the antidepressant effects of exercise in addition to the well-documented cardiopulmonary benefits.

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