Exercise and Pharmacotherapy for Anxiety in Cardiac Patients

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1. Protocol Title: Exercise and Pharmacotherapy for Anxiety in Cardiac Patients: The UNWIND Study

2. Purpose of the Study: Coronary heart disease (CHD) is the leading cause of death in the United States; more than 600,000 Americans suffer a fatal cardiac event each year. Traditional CHD risk factors such as high blood pressure, smoking, and elevated cholesterol do not fully account for the timing and occurrence of CHD events. The term "cardiovascular vulnerable patient" has been used to describe patients susceptible to acute coronary events based upon plaque, blood, or myocardial characteristics. Psychosocial factors also have been shown to be associated with increased adverse health outcomes and increased cardiovascular vulnerability. For example, clinical depression and elevated depressive symptoms are associated with increased morbidity and mortality, and as a result, the American Heart Association has recommended that clinicians should routinely assess depression in CHD patients. Although much research and clinical recommendations have focused on depression, the significance of anxiety has been largely ignored, despite the fact that anxiety disorders are as prevalent as depression in the general population and are associated with similar levels of disability.

Despite the prevalence and prognostic significance of anxiety in CHD populations, there have been few randomized clinical trials (RCTs) specifically targeting anxious CHD patients. Anxiolytic medications, including selective serotonin reuptake inhibitors (SSRIs), have been shown to be effective in treating anxiety. SSRIs have been evaluated for the treatment of clinical depression in cardiac patients, with equivocal results. Surprisingly, to our knowledge, there have been no RCTs examining the efficacy of medications for treating anxiety in CHD patients. Moreover, because many cardiac patients are reluctant to take additional medications and psychotropic medications may not be effective for everyone or may produce unwanted side effects, there continues to be a need to identify alternative approaches for treating anxiety in cardiac patients. We believe that exercise may be one such approach.

The purpose of this study is to evaluate the following hypotheses in a population of CHD patients with elevated symptoms of anxiety. The present study will examine the impact of a 3-month intervention of exercise, Lexapro, or placebo on anxiety symptoms and CHD biomarkers among individuals with cardiac disease and elevated anxiety. We hypothesize the following: (1) Both exercise training and medication will reduce anxiety symptoms to a greater extent than placebo; (2) Exercise training will improve CHD biomarkers of risk including autonomic regulation, vascular endothelial function, and inflammation more than either medication or placebo; and (3) Improvements in CHD biomarkers will be mediated by reductions in symptoms of anxiety. We also will explore potential moderators of treatment (e.g., anxiety diagnoses, CHD severity) as well as the longer-term benefits of treatment by documenting medical events and health care costs over a follow-up period of up to 4 years.

3. Background & Significance: Over $100 billion is spent on CHD each year in direct medical costs, disability payments, and lost productivity.[1] Mental illness also is a major health problem in this country, with estimated direct costs of $57.5 billion in 2006.[2] Mental disorders are associated with significant impairment of function that may, at times, be worse than that of chronic medical disorders. Anxiety disorders are the most commonly diagnosed forms of mental illness in the U.S. and are responsible for one-third of the total expenditures of the federal government for mental illness.[3] Approximately half of those costs are due to the repeated use of health care services since people with anxiety disorders often solicit medical evaluation for symptoms that resemble physical illnesses.[4] Nationally representative surveys indicate that as many as 30% of patients will suffer from some kind of anxiety disorder during their lifetimes,[5] a figure that has increased significantly over the past 2 decades. Anxiety symptoms have been correlated with the presence of one or more chronic diseases,[6] as well as impaired work performance, increased use of medical services, decreased well-being, and lowered functioning.[7, 8] Although the actual prevalence of anxiety disorders among cardiac patients is not known, Tully and Cosh reported an 11-14% prevalence of generalized anxiety disorder (GAD) across 12 studies (N=3485) and a pooled lifetime prevalence of 26%.[9] Frasure-Smith[10] noted that 5.3% of a sample of 804 patients with stable CHD had GAD and 41.4% had elevated anxiety symptoms measured by the Hospital Anxiety and Depression Scale-Anxiety (HADS-A). Thus, anxiety is common in CHD patients. However, the prior

set of reviews raised questions about the significance of anxiety in CHD patients and of the novelty of exercise to treat anxiety. Our team took up this challenge by revisiting and expanding our previous review of the relevant literature and conducting new analyses of pilot data from our laboratory, both of which proved helpful in further articulating a working conceptual model and providing a rationale for our proposed RCT.

Anxiety and CHD Risk. Findings from a number of prospective epidemiological studies report a strong association of anxiety with mortality in healthy individuals [11-13] and in CHD patients.[10, 14-19] Our own studies have shown that elevated scores on the anxiety subscale of the HADS were associated with increased risk of mortality after accounting for established risk factors in 934 men and women with CHD (Hazard Ratio HR , 2.27; 95% CI, 1.55 to 3.33, p<.001).[20] Elevated anxiety symptoms have been shown to be associated with a 2-fold increased risk of mortality in CABG patients[16, 18] and in outpatients with CHD.[10, 21, 22] Frasure-Smith and colleagues reported that CHD patients with GAD assessed two months following hospital discharge showed a 2.3-fold increased risk of adverse cardiac events, and Strik et al.[21] reported a 2.8-fold increased risk of adverse events in acute post-MI patients in which anxiety was measured one month following hospital discharge. Similarly, a 2-fold increased risk of adverse events was observed in stable CHD patients[23] and in patients with elevated anxiety during annual clinic visits.[24] Similar to the depression literature,[25] not all studies have found a prognostic relationship, especially when anxiety was measured in-hospital following an acute coronary event or during diagnostic exercise stress testing.[8, 26-30] In the proposed study, anxiety symptoms will be evaluated outside of the clinic and hospital environment in individuals with stable CHD with high levels of anxiety.

Anxiety and depression share high comorbidity.[10, 31, 32] Findings from several recent prospective studies suggest that anxiety predicts increased risk independently of depression, and that the presence of both anxiety and depression identifies individuals at greater risk of mortality than those with either prognostic factor alone.[20, 33] We observed a 3-fold increased risk of mortality in CHD patients with comorbid anxiety and depression, compared with an approximate 2-fold risk in patients with either anxiety or depression alone.[20] The additive effects of anxiety and depressive symptoms have been noted by other investigators,[33, 34] and we will explore this issue in our proposed trial.

Treatment of Anxiety Disorders in Cardiac Patients. Despite compelling reasons for treating anxiety in CHD patients, there have been few trials that have examined the effects of treating anxiety symptoms in cardiac patients, and no studies reported the effects of treating anxiety on clinical outcomes. Several studies, including the ENRICHD trial, have examined the effects of treating depressed post-MI patients,[35] and several pharmacologic studies have examined the effects of SSRIs on depressive symptoms and outcomes in cardiac patients.[36-40] The SADHART-CHF trial found no advantage for sertraline over placebo in either reducing depression or in improving clinical outcomes.[40] The SADHART study[36] also reported no differences between CHD patients receiving sertraline compared to placebo, although greater reductions in depressive symptoms were observed in the subset of patients with more severe depression. We will consider more severe anxiety (i.e., diagnosed anxiety disorders) as a potential moderator of treatment in our proposed RCT.

Exercise and Anxiety. The use of aerobic exercise has been widely used in many secondary prevention programs[41] and may reduce risk of fatal CHD events.[42] The mechanisms for this benefit remain uncertain, although exercise has been shown to reduce traditional risk factors, such as hypertension and hyperlipidemia,[41] attenuate cardiovascular responses to mental stress and reduce myocardial ischemia,[43-46] and reduce depressive symptoms in patients with MDD,[47] heart failure,[48] and in CHD patients with elevated depressive symptoms.[49] Epidemiological studies have observed an inverse relationship between exercise and anxiety. In a study of 8,098 adults, Goodwin[50] reported that persons who indicated that they exercise “regularly” were at reduced risk for being diagnosed with an anxiety disorder compared to their sedentary counterparts. There have been many exercise trials that have reported anxiety as an outcome.

For example, Wipfli and colleagues[51] found that exercise was associated with an overall effect size of 0.48, indicating greater reductions in anxiety symptoms compared to no-treatment controls, and Herring

and colleagues[52] reported that exercise was associated with an overall effect size of .29, compared to control conditions. In a review of 8 RCTs of patients with a broad range of anxiety disorders, Jayakody[53] noted that exercise seems to be effective as an adjunctive treatment for most anxiety disorders, but there were too few studies to provide meaningful conclusions. In response to the prior review, we re-examined the exercise literature and identified only 12 RCTs specifically targeting patients with high anxiety, most of which had serious methodological shortcomings, including small sample sizes, lack of blinding of assessors, confounding of exercise with other treatments, and no adherence to intent-to-treat analytic principles.[54] In one of the few studies of cardiac patients, Lavie and Milani[55] reported more than a 69% reduction in anxiety among highly anxious participants in an exercise-based cardiac rehabilitation (CR) program; however, there was no control group and exercise was only one component of the intervention. In the one RCT that targeted cardiac patients with elevated anxiety, Oldridge and colleagues reported greater reductions in symptoms of anxiety assessed by the STAI and POMS after 8 weeks of CR compared to community care controls.[56, 57] However, the CR group also received concurrent weekly 90-minute group counseling sessions, including training in progressive relaxation, so that the benefits of exercise training could not be determined. Thus, while results from previous exercise studies are encouraging, there remains an important gap in understanding the potential therapeutic benefits of exercise, especially among anxious cardiac patients who are vulnerable to adverse cardiac events.

Biomarkers of CHD Risk. Reliance on "hard" clinical endpoints (MI and death) that occur infrequently and require large sample sizes over extended follow-up intervals has proven to be a major challenge to furthering our understanding of the optimal ways to treat vulnerable cardiac patients because of the obvious logistical and financial obstacles such investigations present. One solution to this problem is to first study intermediate markers of risk in patients who are vulnerable to untoward cardiac events.[58] Examination of changes in intermediate endpoints can provide important insights into the mechanisms and potential value of clinical interventions and has a number of important advantages over “hard endpoints,” in that fewer patients are required to detect treatment effects and changes in cardiac risk can be reliably and objectively measured over short follow-up intervals. Following the guidelines advanced by a panel of prominent cardiovascular scientists,[59, 60] we propose to examine intervention effects on autonomic, vascular, and inflammatory biomarkers of cardiovascular risk (i.e., "intermediate endpoints") in “vulnerable” CHD patients with high anxiety:

Heart rate variability (HRV) is widely recognized as an important index of autonomic regulation of the heart and prognostic indicator of risk and will serve as our primary biomarker of interest. Reduced 24-hour HRV independently predicts mortality in community samples[61-63] and patients with stable CHD,[64] with a recent MI, [65] or with heart failure (HF).[66]

Baroreceptor reflex sensitivity (BRS) is also an index of cardiac regulation by the parasympathetic nervous system (PSNS), with experimental models showing that low levels of BRS predict sudden cardiac death (SCD) due to ventricular fibrillation.[67] Anxiety has been linked to reduced PSNS control of heart rate in several different populations, including patients with anxiety disorders,[68-72] MDD, [73, 74] and CHD,[75] as well as healthy volunteers.[76] Elevated sympathetic nervous system (SNS) activity is another pathophysiological aspect of autonomic dysregulation contributing to the development of CHD[77] that is thought to contribute to increased cardiovascular risk associated with anxiety.[78, 79]

Although no study has compared the effects of an SSRI with exercise training on HRV in anxious cardiac patients, it is well documented that SSRIs that inhibit the reuptake of norepinephrine reduce HRV.[80, 81] Several RCTs have provided evidence that regular exercise improves HRV, as well as BRS, in middle-aged and elderly sedentary subjects[82, 83] and patients with CHD. In the present proposal, 24-hour HRV will be our primary biomarker in examining the impact of exercise and anxiolytic medication on cardiovascular risk in anxious CHD patients, with SNS activity also assessed in order to provide a comprehensive assessment of intervention effects on autonomic regulation.

Endothelial dysfunction plays a vital role in the development, progression, and clinical manifestations of atherosclerosis.[84, 85] It can be assessed non-invasively using standardized vascular ultrasound techniques to determine flow-mediated dilatation (FMD) of the brachial artery,[86] has been

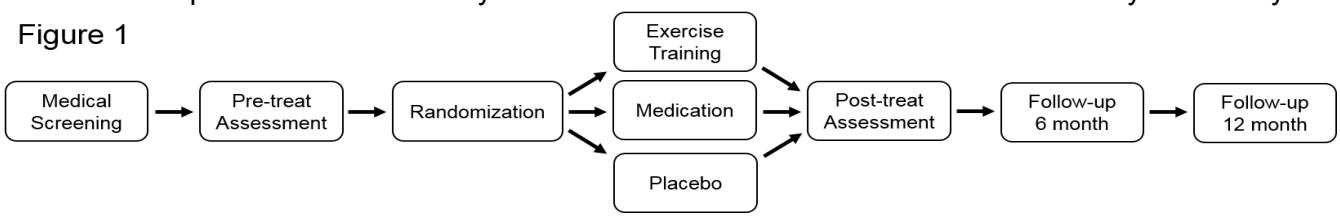
related to a wide range of CHD risk factors,[87] and has been shown to be prognostic in cardiac patients. Impaired FMD has been linked to elevated depression symptoms in stable CHD patients,[88] and to elevated anxiety symptoms in CHD patients following a percutaneous coronary intervention.[89] Several studies also have shown that acute mental stress is associated with impaired FMD.[90-92] There is preliminary evidence that exercise may improve endothelial function in CHD patients. Several cross-sectional studies have found that self-reported physical activity is associated with preserved endothelial function.[93, 94] Several small interventional studies also have shown that FMD may be improved by exercise training in cardiac patients.[95-98] These observations suggest that reducing anxiety symptoms may result in improved FMD and that anxious CHD patients randomized to the exercise intervention may demonstrate the most marked improvements in FMD.

Inflammation is widely considered to play a central role in the development and progression of CHD. C-reactive protein (CRP), an acute-phase reactant primarily produced in hepatocytes, is a highly sensitive marker of underlying systemic inflammation.[99] An elevated level of CRP is an independent risk factor for MI and stroke.[100, 101] Interleukin-6 (IL-6) is an inflammatory cytokine that may be the initial event leading to an increase in CRP levels, and recent meta-analyses indicate that IL-6 may be more strongly related than CRP to the promotion of atherosclerosis.[102, 103] Elevated levels of both CRP and IL-6 have been observed in patients with depression,[104-106] but few studies have examined the relationship with anxiety.[107] In a subsample of healthy participants in the ATTICA study, Pitsavos et al.[108] observed a significant dose-response relationship between the severity of anxiety symptoms and CRP and IL-6. In a cross-sectional study of 120 stable CHD outpatients, Bankier et al.[109] also found GAD to be associated with increased CRP. In a sample of 682 post-ACS patients, Frasure-Smith et al.[110] reported that HRV was correlated with inflammatory markers and suggested that interventions targeting regulation of both autonomic control and inflammation may be especially worthwhile. The interventions proposed in this RCT are designed to accomplish this goal.

Summary. We propose to examine the effects of exercise and anxiolytic medication on both symptoms of anxiety and on "intermediate endpoints" that are associated with adverse outcomes in CHD patients. In this application, we propose a RCT to compare the effects of exercise training and anxiolytic medication (escitalopram, Lexapro) to a placebo in anxious patients with CHD. Patients will be assessed on clinical, behavioral, and physiological dimensions at baseline, 3 months (post-treatment), and 6-month follow-up. Additional measures of quality of life also will be obtained along with annual follow-ups to document clinical events and medical costs. The findings from this RCT will have directly translational implications for anxiety assessment and management in CHD patients.

4. Design & Procedures: This study will be a single-site, randomized clinical trial of exercise training and anxiolytic medication in the treatment of anxiety in anxious CHD patients without MDD as a primary diagnosis. One hundred fifty men and women aged ≥40 years with stable CHD and elevated anxiety symptoms (HADS-A scores ≥11) will be randomly assigned to Exercise Training, Medication (escitalopram), or Placebo. Patients will be evaluated for anxiety at baseline, after 3 months of treatment, and at 6-month and annual follow-ups. Three months is ample time to observe cardiovascular conditioning effects, even among older cardiac patients, whose responses are often quite variable, and is also adequate to assess the efficacy of pharmacologic treatment. Comprehensive assessments will include clinical evaluations of anxiety and measures of intermediate surrogate endpoints, including autonomic, vascular, and blood markers of risk. Following the completion of the 3-month treatment program, subjects will undergo a post-intervention repeat assessment. Patients will then undergo a 6-month follow-up evaluation for anxiety and CHD risk status and will be followed annually for anxiety and

Figure 1



clinical events (see Figure 1). All assessors will be blinded to patients' treatment group assignment; groups receiving a pill will be double-blind. Following completion of the intervention, participants will be advised to contact their referring physicians, if necessary, for further treatment, or they will be referred to appropriate mental health care providers.

I. Assessment of Anxiety

Patients will undergo a comprehensive assessment of anxiety. The primary outcome measure will be scores on the Hospital Anxiety and Depression Scale – Anxiety (HADS-A).[111] The HADS-A is a commonly used psychiatric self-report questionnaire designed to identify anxiety and depression among patients in nonpsychiatric medical settings,[112] and has been shown to detect independent constructs of anxiety and depression.[111, 113, 114] It has excellent psychometric properties,[111, 113-117] and has been widely used in outpatient RCTs in patients with clinical anxiety.[118, 119] Published clinical cutoffs[120] are 0-7 (normal), 8-10 (mild), 11-14 (moderate), and 15-21 (severe). Our eligibility criteria will include patients with HADS-A scores ≥8, which represents a more conservative cut-point for identifying patients with significant anxiety who are at increased risk for adverse CHD events and who may receive greater benefit from treatment.

A clinical psychologist will administer modules from the Structured Clinical Interview for DSM-5 Disorders (SCID), including the anxiety disorder section, the mood disorder section (to rule out primary MDD), the somatization section, and the alcohol abuse and/or dependence section.[121] The psychologist also will administer the 14-item Hamilton Anxiety Rating Scale (HAMA)[122] to obtain a clinical rating of anxiety symptom severity.

Other psychiatric self-report anxiety assessments will include the Anxiety and Depression Detector (ADD), the Patient Health Questionnaire 9 item (PHQ-9), the Anxiety Sensitivity Index (ASI), and the General Anxiety Disorder 7-item questionnaire (GAD-7). Together, these assessments will afford a comprehensive analysis of a patient's severity of anxiety symptoms and the comorbidity with depression. The ADD provides 5 items that effectively and efficiently screen for panic disorder, PTSD, social phobia, GAD, and depression.[123] The PHQ-9 is a brief, reliable, and valid measure of depression severity.[124] The ASI assesses fear of arousal-related sensations, and we will be using the test to assess physical factors of arousal.[125] The GAD-7 is an efficient screening tool for assessing GAD severity.[126]

The 20-item Trait section of the Spielberger Stait-Trait Inventory (STAI) also will be presented to the patients to assess anxiety symptoms before treatment. However, to assess ongoing treatment response, participants will complete the 20-item State section of the STAI[127] at weekly intervals throughout the duration of the 3-month intervention by a clinician who will be blinded to patients' treatment group status. The STAI will be used to evaluate the process of change and to assess at-risk patients (i.e., worsening anxiety) regularly and systematically. Suicidal potential also will be carefully assessed. Contact time will be documented and content limited (to avoid simulating psychotherapy, which would seriously confound data interpretation).

Importantly, patients with primary MDD will be excluded from this trial. However, because symptoms of depression are likely to co-occur with anxiety, we also will assess depressive symptoms with the Beck Depression Inventory-II (BDI-II).[128] The BDI-II is a widely used measure of depressive symptomatology, consisting of 21 items, each corresponding to a specific category of symptoms and attitudes. It has been shown to be both a reliable and valid measure of depression severity[129] and has been used in many major interventional trials of cardiac patients.[35, 130, 131] Item #9 (suicidality) of the BDI-II will be used to assess suicidal ideation and administered weekly along with the STAI.

Electronic-based questionnaires (e-questionnaires) will be used for all assessments, both anxiety and quality of life, except for interview-based assessments. These e-questionnaires will be delivered during participants' visits to Duke for pre- and post-intervention assessments. A Duke Psychiatry computer will be used and secured by Psychiatry Computer Support. The computer log-in will be performed and documented by study personnel; the computer will be used only for the survey purpose;

the study personnel will remain in the room with the participants while they have computer access; and study personnel will document log-off before leaving the room. The computer will be setup such that only necessary software will be installed on the computer, and access to other applications and network assets will be limited. The software necessary for assessments is Qualtrics, a Duke-approved survey platform.

II. Intermediate Endpoint Assessments

1. Heart Rate Variability. For the 24-hour HRV measurement, patients will be instrumented with a DigiTrak XT Holter ambulatory ECG monitor (Philips Healthcare, Andover, MA). Following instrumentation, patients will be reminded to engage in their normal pattern of activity and to wear the monitor for 24 hours. During that time, if participants experience a high-anxiety event, they will be asked to record the event by pressing an event marker button associated with the monitor. A Laser scanner (DelMar Medical, Irvine, California, USA) will be used to scan the recordings using standard Holter analysis procedures. The labeled beat-to-beat file will then be processed using the DelMar time domain HRV analysis software and the DelMar enhanced 24-hour spectral heart rate variability analysis software. Heart rate variability will be estimated from the standard deviation of all normal R-R intervals (SDNN) and from spectral power summed across each of the following bands: high frequency (0.14 to 0.5 Hz), low frequency (0.05 to 0.139 Hz), very low frequency (0.003 to 0.049 Hz), and ultra-low frequency (0.000015 to 0.0029 Hz). For the purposes of the proposed study, the primary hypotheses will be tested using the SDNN measure of HRV, because it is less affected by artifact and nonstationarities found in the ambulatory environment and is most strongly predictive of increased risk of mortality.[65] Certain medications may affect HRV through effects on the autonomic nervous system. Beta-blockers, for example, are known to increase the tonic levels of several measures of HRV, such as RSA. However, the primary outcome HRV measure, SDNN, is relatively resistant to the effects of beta-blockade.[132] Because sleep apnea may impact HRV, a STOP-BANG sleep apnea questionnaire will be administered.

2. Baroreflex Sensitivity. BRS studies will be performed between 0800 and 1000 hours under fasting conditions. In the supine posture, following 5 minutes of quiet rest, 10 minutes of beat-to-beat BP data will be collected using the Finometer PRO Model-1 (Finapres Medical System, Amsterdam, the Netherlands), and 10 minutes of beat-to-beat R-R interval will be collected from an electrocardiogram (ECG) recorded digitally at 1000 Hz. The Finometer instrument utilizes the vascular unloading technique to measure SBP, DBP, and MAP on a beat-to-beat basis, and has been validated against intra-arterial measures under various conditions.[133] Power spectra will be estimated using the Welch algorithm.[134] Power spectra will be derived as the average of 60-second data segments, overlapping by half. BRS will be estimated from the modulus of the cross spectrum of R-R interval and SBP for frequencies ranging from 0.070 - 0.129 Hz. This method produces reliable measures that are comparable to estimates of BRS obtained using the invasive phenylephrine injection technique, widely considered to be the “gold standard” measurement method.[135]

3. Vascular Endothelial Function. Our approach for assessing endothelial function conforms to the recently published guidelines for assessment of flow-mediated arterial vasodilatation.[136] Longitudinal B-mode ultrasound images of the brachial artery, 4-6 cm proximal to the antecubital crease, will be obtained at end-diastole (ECG R-wave gated digital image capture) using a dedicated Acuson Aspen ultrasound platform. All images will be acquired with participants supine, utilizing an 11 MHz linear array probe with stereotactic holder in our temperature-controlled clinical research laboratory, by Michael Ellis, RDMS, RVT, who has over 15 years of experience performing the standardized image acquisition protocols for our ultrasound FMD assessments. In an unpublished evaluation of 20 healthy men and women who underwent our FMD assessment protocol on two consecutive days, repeat FMD values showed a correlation of $r=0.81$, $p<.001$, a mean absolute difference of 0.64%. Images will be obtained and stored digitally at resting baseline, as well as during and following inflation to 250 mm Hg of an occlusion cuff placed around the forearm, 2 cm below the elbow. All arterial diameter measurements will be performed by the same experienced member of the research team (AS), blinded to participant identity and treatment condition, using edge detection software (Brachial Analyzer, MIA-LLC, Coralville, IA). FMD response will be assessed from 10-120 seconds post-deflation of the forearm cuff, with peak arterial

diameter quantified using polynomial curve fitting, and FMD thereby defined as the maximum percent change in arterial diameter relative to pre-inflation resting baseline. As others have reported, using this rigorous standardization of FMD methodology, our FMD assessments will be obtained with optimal reproducibility, reflected in a coefficient of variation of approximately 10% or less.[137-139] Peak hyperemic flow and shear stress will be derived by standard formulae based upon Doppler velocity measurements during the first 10 seconds following deflation of the occlusion cuff.[140],[141] In participants for whom there is no contraindication (e.g., history of migraine), we also will assess brachial artery response to the administration of 0.4 mg sublingual glyceryl trinitrate (GTN), which is the standard approach to confirming vascular endothelial specificity of FMD findings.[86]

4. Measures of chronic inflammation. Plasma inflammatory biomarkers will be measured by ELISA using commercially available kits. We will examine C-Reactive Protein (hsCRP) using a high-sensitivity assay obtained from American Diagnostica, Inc. (Stamford, CT). We will also measure interleukin-6 (IL-6), an inflammatory cytokine that promotes myocardial hypertrophy and may be elevated prior to increases in CRP levels. On the day of blood work, we will ask participants to hold off taking nonsteroidal anti-inflammatory medications (including aspirin) and antihistamines until after their morning (0700-0800 hours) blood draw.

5. Urinary catecholamines. Patients will be asked to collect urine over a 24-hour period, with samples kept cold by storage in a portable cooler. Samples will be assayed for norepinephrine, epinephrine, creatinine, sodium, and potassium. Catecholamine levels will be expressed as urine concentration (μg/ml) per urine concentration of creatinine (mg/ml), yielding norepinephrine and epinephrine values in units of μg per mg creatinine for each sample. This provides catecholamine excretion indices that are corrected for individual differences in body size and urine volume.[142] In prior studies, urinary catecholamine data have proven informative, with low subject burden and excellent compliance.[78, 143, 144] As in these prior studies, excellent compliance with urine collection is achieved by emphasizing to participants the importance of a complete 24-hour collection and by providing detailed instructions on how this can be achieved. The completeness of 24-hour urine collections will be assessed by ascertaining whether 24-hour urinary creatinine excretion falls within boundaries based upon body size, race and gender.[145] Incomplete collections will be repeated.

6. Lipids. Total cholesterol, HDL- and LDL-cholesterol, VLDL-cholesterol, and triglycerides will be assayed from fasting blood samples drawn between 0700 and 0800 hours.

7. Metabolic blood analyses. Other blood components to be analyzed include a metabolic panel, insulin, and HbA1c.

8. Blood biomarker analyses. Participant blood that remains following the aforementioned blood analyses may be banked for potential future analyses examining blood biomarkers, such as proteins or metabolites, related to the interplay of exercise, anxiety, and cardiac disease. Importantly, the ability to bank participants' extra blood is at the discretion of the participants. During the consenting process, participants will be explicitly informed about this optional sub-study, their ability to choose whether or not their blood may be saved, and that their choice does not influence their participation or treatment in the study. Participants will consent by initialing a specific section of the consent form detailing the storage and use of their blood.

III. Assessment of Aerobic Capacity

Graded treadmill exercise testing will be conducted at baseline and at the conclusion of treatment using a protocol developed at Duke and Wake Forest Universities.[146] Subjects will exercise to exhaustion or other standard endpoints (e.g., chest pain, ST-segment depression, etc.) under continuous electrocardiographic monitoring. Expired gases will be analyzed continuously by a Parvo Medics True One measurement system (Parvo Medics, Sandy, Utah). Peak VO_2 will serve as the primary measure of aerobic capacity.

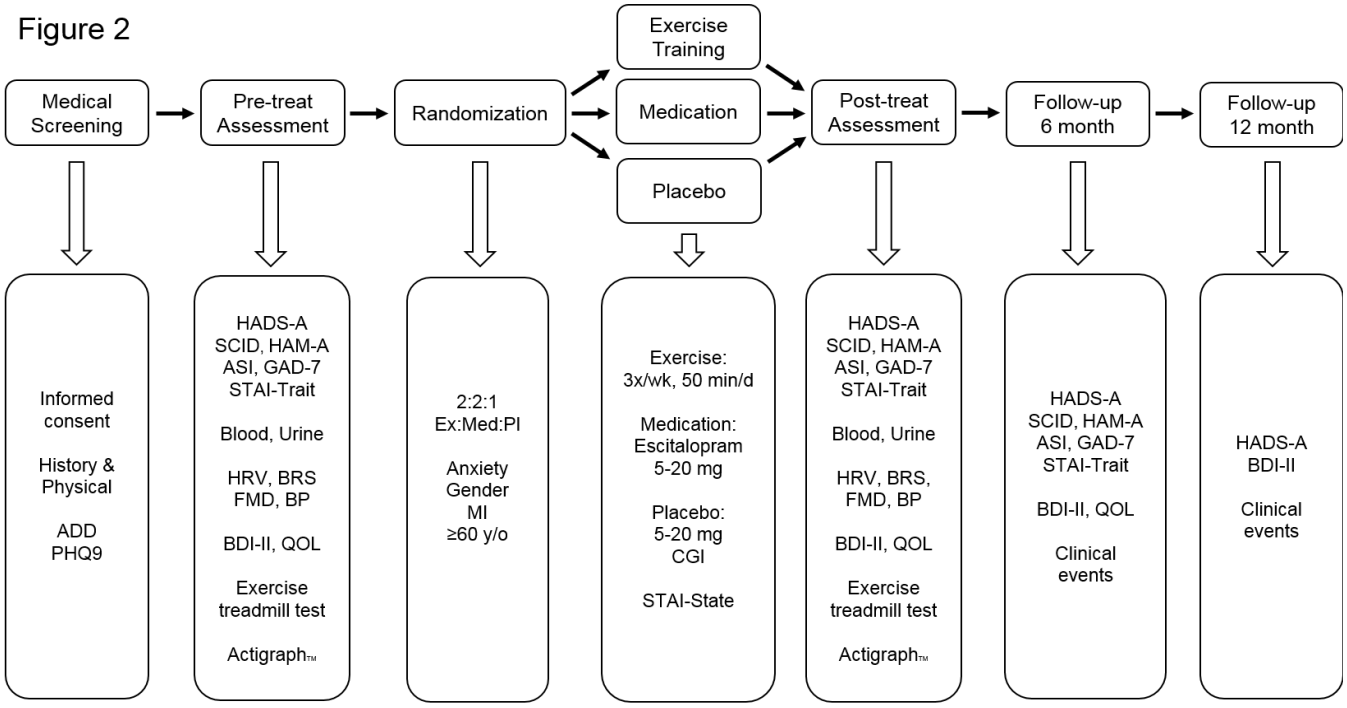
To obtain a measure of participants' average daily physical activity, participants' will be asked to wear an Actigraph$_{TM}$ activity watch for 7 continuous days. The Actigraph$_{TM}$ GT9X Link features a validated 3-axis accelerometer, and the accompanying software allows for examination of physical activity

characteristics and sleep patterns.

IV. Assessment of Quality of Life

The proposed interventions may not only reduce anxiety, but also impact a number of other areas of functioning that are considered to reflect "quality of life." We propose to use a questionnaire battery that includes a measure of general health,[147] resilience,[148] perceived stress,[149] optimism,[150] self-efficacy, and perceived social support.[151, 152] These are clearly exploratory measures and are peripheral to our main hypotheses. However, this information is of interest and can be obtained at minimal additional cost. Further, to obtain a more complete picture of patients' health, we also will use the Godin Leisure-Time Exercise questionnaire[153] to evaluate exercise habits, the Pittsburgh sleep questionnaire[154] to examine sleep patterns, which may affect anxiety and HRV, the Morisky Medication Adherence Scale[155] and Medication Adherence Behavior Evaluation to identify medication adherence, and a fat-related diet habits questionnaire[156] to examine nutrition habits.

Figure 2



ADD, Anxiety and Depression Detector; PHQ9, Personal Health Questionnaire; HADS-A, Hospital Anxiety and Depression Scale – Anxiety; SCID, Structured Clinical Interview for DSM-5 Disorders; HAM-A, Hamilton Anxiety Rating Scale – Anxiety; ASI, Anxiety Sensitivity Index; GAD-7, General Anxiety Disorder-7 item; STAI, Spielberger State-Trait Anxiety Inventory; HRV, Heart rate variability; BRS, Baroreceptor sensitivity; FMD, Forearm mediated dilation; BP, Blood pressure; BDI-II, Beck Depression Inventory-II; QOL, Quality of Life assessments; Actigraph™, wrist accelerometer; CGI, Clinical Global Impressions Scale.

V. Post-treatment Assessments at 3-Months and at 9-Months (Six-month follow-up)

At the conclusion of the 3-month intervention (post-treatment), or at the time a participant may drop out of the study (or in the rare instance of requiring additional or different anxiolytic treatment outside of our protocol), patients will complete the same clinical, biomarker, and psychometric test battery that they completed at baseline. At the 6-month follow-up, we will assess anxiety, patients' exercise habits, any psychiatric treatment, psychopharmacologic medications, aerobic fitness using a 6-minute walk test, and cardiac status, including revascularization procedures and CHD events. This will be a naturalistic follow-up that we have used in previous trials,[157, 158] which will allow us to determine patients' anxiety status 6 months after the conclusion of study-related treatment, along with changes in health habits and measures of quality of life. Figure 2 presents an expanded view of the assessment schedule and design of the study. For clinical events, we carefully will document cardiac-related hospitalizations and

emergency room visits, revascularizations, and any deaths for up to 4 years post-treatment.

Both pre-treatment and post-treatment (3 month) assessments will be performed in the same sequence over 3-4 visits. Following a phone screen, participants will arrive for Visit 1 under normal physiologic conditions (i.e. not fasted and having taken all medications) for an orientation and consenting process. If participants consent to the study, then they will perform the battery of anxiety and quality of life assessments and the physical. For Visit 2, participants will arrive fasted and bring in their medication(s). Blood will be taken followed by HRV and BRS measurements and Holter monitor set-up. After these fasted-required procedures are performed, we will provide food for the participants so they can take their medicine. Then, the Actigraph will be initialized and put on participants' wrists, and they will be given a urine cup to take home. For Visit 3, participants will arrive under normal physiologic conditions except for taking aspirin, NSAIDs, or other medication that will impact vascular dynamics. Participants will return the Holter monitor, Actigraph, and urine cup. Lab procedures will include tests for vascular endothelial function, consisting of forearm-mediated dilation, and aerobic capacity, consisting of the exercise treadmill test. Based on the participants' schedules and time limitations, they may choose to combine Visit 2 and Visit 3. On Visit 4, participants will arrive under normal physiologic conditions. Participants will be randomized. If randomization is to a pill group, participants will immediately visit Dr. Wei. If randomization is to exercise training, participants will immediately meet with a staff exercise physiologist to discuss exercise prescription and exercise site location.

VI. Annual Follow up for Clinical Events

Medical outcomes will be tracked. Our main medical outcome is combined all-cause mortality and CHD hospitalizations, emergency department visits, and unscheduled physician office visits because of worsening angina. The study staff will collect these data via medical records review, which will be coordinated by Dr. Alan Hinderliter at UNC. We have conducted these types of follow-up assessments in our prior work.[159, 160] Based upon unpublished data from our UPBEAT trial, it is estimated that there will be a 30% annual event rate in this vulnerable population of anxious CHD patients.

5. Selection of Subjects: This will be an outpatient study of 150 cardiac patients with stable CHD and elevated symptoms of anxiety. We anticipate consenting 300 patients in order to reach our goal of 150 randomized. To accomplish our recruitment and treatment goals, we have established a referral network of community hospitals including Duke University Medical Center, the Durham Veterans Affairs (VA) Hospital, Duke Raleigh Hospital, Alamance Regional Hospital, WakeMed Health and Hospitals, and the UNC Health Care system in Chapel Hill. Patients will be recruited through a variety of sources including IRB-approved advertising, such as brochures, flyers, e-mail messaging, posters, television, radio, and internet, like researchmatch.org. Additional recruitment aids include self-referral and referral from physicians, psychologists, and other mental health care professionals. We also my mail letters to participants of our previous studies, including but not limited to ENHANCED (Pro00015896), UPBEAT (Pro00011980), and REMIT (Pro00009555), that inform the patients about the opportunity of this study; these letters first would be IRB approved through the previous studies protocol and then through this study's protocol before being mailed. Further, potential participants may be identified by reviewing records from Duke Cardiopulmonary Rehabilitation and UNC Cardiopulmonary Rehabilitation and Duke Echocardiography Laboratory. Further still, potential participants may be pre-screened through Maestro Care; upon identifying potential participants, we first would contact the physicians of the potential participants to acquire their consent to inform their patients about the study. This approach effectively serves to avoid "cold calling" participants. Following agreement by the physicians and a positive acknowledgement by their respective patients, we would inform the patients about the study. Finally, following physician consent, we may identify potential participants by reviewing physician records and meet the identified patients in the clinic; this meeting would take place after the patient's physician introduces the study and gains the patient's acknowledgement to receive more study information, and the meeting purpose would be to describe the study and, if the patient is interested, present a short consent form to the patient that is directed to taking the 2-item GAD questionnaire to determine anxiety

symptom severity and, thus, study eligibility. This is a racially and socioeconomically diverse region, which will be reflected in our sample of anxious CHD patients. Patients from Duke, UNC, and outside hospitals will be considered for participation. Non-Duke patients will be provided with Duke's Notice of Privacy Practices.

Inclusion criteria. Men and women with documented CHD (i.e., a prior MI, coronary revascularization procedure, or >70% stenosis in at least one coronary artery) age ≥40 years will be selected for study. Patients also will have an anxiety symptom severity score of ≥8 on the HADS-A; a subgroup of patients will also have a DSM-5 diagnosis of an Anxiety Disorder. A modified GAD diagnosis will be used, wherein the GAD criteria include a minimum of 1 month of worry and at least 2 of the associated symptoms listed in DSM-V. Patients diagnosed with MDD may be included provided a) they have an anxiety diagnosis (e.g., generalized anxiety disorder, panic disorder, social anxiety disorder); b) their BDI-II total score is < 30; c) their response to BDI-II item #9 (suicidality) is 0 or 1; and d) the psychiatric interview determines that the patient is at minimal suicide risk.For patients included that meet these criteria, suicidality will be assessed weekly throughout the duration of the trial as noted in Section 13 (Data and Safety Monitoring). We plan to actively recruit women and minorities, with at least 50% women and 25% minorities.

Exclusion criteria. Medical exclusions will include an MI or coronary revascularization procedure (i.e., CABG or percutaneous coronary intervention) within the last 3 months, unstable angina, severe left ventricular dysfunction or decompensated heart failure (i.e., left ventricular ejection fraction <30% AND New York Heart Association functional classification of III or IV), unrevascularized left main coronary artery stenosis >50%, pacemaker dependence, resting BP >200/120 mm Hg, and conditions that would preclude randomization to either the drug (e.g., prolonged QT interval, known allergy to or intolerance of escitalopram) or exercise (e.g., musculoskeletal problems or abnormal cardiac response to exercise). Patients with a primary psychiatric diagnosis other than Anxiety Disorder will be excluded, including patients with MDD, PTSD, OCD, or any of the following DSM-5 diagnoses: 1) Dementia, delirium; 2) Schizophrenia, Schizoaffective, or other psychotic disorder; 3) Psychotic features including any delusions or hallucinations; or 4) Current alcohol or other substance abuse disorder. Further, patients with active suicidal ideation at screening and/or a history of a suicide attempt requiring inpatient admission will not be enrolled into the trial. To determine the risk for suicide, which would meet our exclusion criteria, any patient with a history of inpatient admission for MDD documented in the medical record will be excluded. Second, selection of BDI-II response choice 2 ("I would like to kill myself") or 3 ("I would kill myself if I had the chance") to BDI-II item 9 would be excluded. Similarly, patients who pose an acute suicide or homicide risk or who, during the course of the study, would likely require treatment with additional psychopharmacologic agents will not be enrolled. Patients will also be excluded if they are taking other medications that would preclude assignment to either drug or exercise conditions (e.g., clonidine, dicumarol, anticonvulsants, and MAO inhibitors) or are taking herbal supplements with purported mood effects (e.g., St. John's Wort, valerian, ginkgo). Patients already engaged in regular exercise (at least 30 minutes >1x/week) will not be enrolled. Finally, pregnant women will be excluded from participation.

I. Screening procedures

1. Psychiatric Screen. All potential candidates will be screened using the ADD[123] and the PHQ-9. The ADD is a 5-item instrument that has been used to detect anxiety (and depression) in medical settings and is an effective screening tool for anxiety disorders (e.g., panic disorder, social phobia, and GAD). It is a good overall measure of distress and is likely to reflect a diagnosis of at least one of these conditions or at least significantly elevated levels of anxiety. Patients must obtain a score of ≥1; the ADD is correlated with the Overall Anxiety Severity and Impairment Scale (OASIS),[161] which also has been used to detect the presence of significant anxiety. The PHQ-9 is a brief, reliable, and valid measure of depression severity (J Gen Intern Med. 2001; 16:606-613), which will be used to examine the comorbidity between anxiety and depression in patients.

2. Medical Screen. Each participant will receive a screening physical examination. Blood pressure (BP) will be determined by standard sphygmomanometry. Subjects will undergo routine blood

tests including creatinine, electrolytes, liver function tests, complete blood count, B12, insulin, and thyroid profile, which will be performed by phlebotomy-trained study staff. If subjects are found to have any significant medical illness during the medical screen that would contraindicate safe participation in this study, they will be excluded. Because older cardiac patients are likely to have at least one additional chronic disease, the presence of a comorbid medical condition is not, in itself, a reason for exclusion. Smoking and alcohol use also will be documented at screening, as well as during follow-up.

6. Subject Recruitment and Compensation: One hundred fifty anxious CHD patients (approximately 50% women and 25% minority) will be recruited from the North Carolina Piedmont region. Because children are unlikely to suffer a cardiac event, and age (and CHD risk factors) is strongly related to our intermediate endpoints, children will not be included in our proposed investigation. The catchment area from which we draw our research subjects encompasses the counties of Durham (pop. 192,566; 50% minority), Orange (pop. 104,186; 25% minority), Chatham (pop. 42,985; 21% minority), Alamance (pop. 115,278; 20% minority), and Wake (pop. 518,206; 23% minority). We believe that recruitment from this geographic area will allow us to enroll sufficient minorities and patients from diverse socioeconomic backgrounds. It also should be noted that approximately 4,000 patients with suspected CHD are catheterized each year at Duke, with 70% (2,800 patients) having stenoses of >75% in at least 1 artery. At the Durham VA, 600 patients are catheterized annually, with 90% having CHD. More than 1,200 patients undergo cardiac catheterizations at UNC, and more than 2,000 patients with stable CHD are in the UNC Health Care Network. Thus, there is an ample recruitment base for potential patients for this study.

In addition to receiving free evaluations and treatment programs, subjects will be compensated with $125 for completing the study. And as a token of our appreciation for participation, and as a method of promoting participant engagement in the trial, we will send birthday and holiday cards to participants.

7. Consent Process: Informed consent will be obtained during interviews between potential subjects and a member of the investigational team familiar with all aspects of the project.

8. Subject's Capacity to Give Legally Effective Consent: Subjects who are <18 years of age or with diminished capacity will be excluded.

9. Study Interventions:

Randomization: All eligible subjects will be randomly assigned to one of the 3 treatment conditions. Randomization will occur after each subject has completed the assessment protocol and will adhere to standard procedures for randomized clinical trials.[162] We will employ a conditional randomization procedure wherein equal proportion of participants with anxiety disorders will be assigned to the respective treatment groups. We also will stratify by gender (male/female), history of myocardial infarction (yes/no), and age (<60/≥60). Our anticipated sample size is 150 patients, wherein randomization will include 60 patients to Exercise Training, 60 patients to Medication, and 30 patients to Placebo. We anticipate needing to consent 300 patients in order to reach our sample size goal.

1. Supervised aerobic exercise. Patients will exercise three times per week, under medical supervision, at a level of 70-85% of their VO_{2peak} as determined at the time of their baseline exercise treadmill test. Patients' exercise will consist of 10 minutes of gradual warm-up exercises followed by 35 minutes of continuous walking, biking, or jogging, and 5 minutes of cool down exercises for a total a 50 minutes per session. Patients will be instructed to monitor their radial pulses and will be checked at least three times per session to ensure that they are within their prescribed exercise training ranges. Weekly supervised exercise sessions may take place at one of four sites chosen by the patient: Duke Cardiopulmonary Rehabilitation at Croasdaile, WakeMed Health and Hospitals, UNC Wellness Center at Meadowmont, and Alamance Regional Medical Center. Although depending on the geographic location of participants, other sites may be recruited for participation.

At UNC Wellness Center at Meadowmont, Dr. Hinderliter will oversee recruitment and exercise interventions, provide active consultation and collaboration in all aspects of the study, and contribute to data analysis and manuscript writing, while Dr. Miller will assist with recruitment and oversee participation of subjects. Both investigators will have access to Duke PHI. At WakeMed, Beth Drossman and staff will work in their normal capacity to supervise patient exercise. At Alamance Regional Hospital, now owned by Cone Health, Jamie Athas will work in her normal capacity to supervise patient exercise.

2/3. Medication/placebo. Treatment in the medication and placebo pill arms will be supervised by Dr. Wei Jiang. Drug dispensing will be performed by licensed pharmacists at the Duke Investigational Drug Services, who have extensive experience in clinical trials. The pharmacists will maintain the blind and will dispense enough medication/placebo to last until the next visit. Each bottle will have a label displaying the dose and the subject ID number of the patient who is to receive the medication/placebo. We will use the SSRI escitalopram (Lexapro), which has received FDA approval for the treatment of anxiety, in 5 mg capsules or matched placebo. Medication will be dispensed as capsules of escitalopram or placebo in individually coded bottles. A new bottle of medications will be dispensed at each medication dispensing visit to study staff. Medication will be taken once daily in the morning but can be switched to once daily in the evening if deemed necessary. Medication adherence will be assessed using pill count at each study visit. Medication adherence, defined as the percentage of days on which the medication was taken, will be compared between the two pill arms to determine whether group differences in HADS-A scores could be attributed to differences in medication adherence.

Patients will see Dr. Jiang (who will be blinded to pill condition) at week 0 (baseline), week 1, week 2, week 4, week 8, and week 12 with phone consultations at weeks 3 and 6. Patients will be contacted weekly by telephone between regularly scheduled visits to take the STAI-State. Dr. Jiang will make all medication adjustments based primarily upon STAI scores and safety/tolerability/side-effect assessments. Patients will be randomly assigned to receive escitalopram (5 mg/d) or placebo. Depending on symptoms, daily escitalopram (or placebo) doses will be titrated to 10 mg after week 2 and to 15 mg or placebo equivalent at week 3 if patients show no change or only minimal improvement. At week 4, if patients show no change or only minimal improvement, they will receive up to a maximum daily dose of 20 mg or placebo equivalent. The dose can be reduced in the event of side effects. Dr. Jiang is an experienced clinical investigator in pharmacological RCTs and will serve as the treating psychiatrist for this trial. In all cases, the treating physician will use supportive measures to help manage medication side effects. In cases of severe side effects or patient discomfort, the physician may elect to decrease the medication dosage at any time or permit unscheduled visits during the study. At each medication dispensing visit, the patient will see the treating physician, who will prescribe the medication, and the study coordinator, who will order the medication, which will be signed off by the treating physician. The signed order will be released to and filled by the on-site investigational pharmacy. The pharmacy will dispense enough medication to last to the next expected dispensing visit plus a 5-day window. Patients will be instructed to use their previous bottle of medication before opening and using the newest provided bottle(s). The pharmacy will be responsible for medication storage and verifying expiration, maintaining the blind, storing codes in a sealed envelope accessible at emergencies, and for dispensing medication.

Patients and raters will be kept blinded to drug therapy assignments both during the treatment phase (3 months) and until the patient has completed the post-treatment assessments. Dr. Jiang, who will perform the ongoing medication monitoring and safety ratings, will be blinded until the completion of the trial. Limited use of sleep medications, but not other anxiolytic agents, will be permitted (see Human Subjects).

10. Risk / Benefit Assessment: Potential risks and minimizing potential risks: Procedures for protecting subjects against potential risks include the careful screening procedure outlined in the application, weekly anxiety monitoring of all patients by a trained clinical psychologist, and the attendance of qualified personnel at all exercise testing and training sessions. The treatment duration is sufficiently brief (3 months) to permit a placebo-controlled trial and yet is of adequate duration to produce therapeutic

benefits.

The favorable efficacy profile with low incidence of side effects has led to SSRIs being the most frequently prescribed class of medications for treating anxiety disorders. After consultation with a number of experts in the psychopharmacological treatment of anxiety disorders, including our collaborator, Dr. Jonathan Davidson, we ultimately selected the FDA-approved SSRI anxiolytic agent escitalopram for this study, because it is among the more selective serotonin re-uptake inhibitors, has an optimal profile for safety and effectiveness in the treatment of anxiety disorders, and it has been used safely in cardiac patients in a variety of studies.

Escitalopram also has been investigated across a range of anxiety disorders and has been found to be safe for elderly persons with CHD and central nervous system (CNS) disorders (e.g. dementia, stroke). Multiple studies have demonstrated that SSRIs are effective in improving various anxiety symptoms in animal models and individuals who do not have formally diagnosed anxiety disorders based on DSM criteria. The effects of escitalopram on GAD and other anxiety disorders have been well-demonstrated in a variety of RCTs. Owing to multiple metabolic degrading pathways, the clinically relevant interactions of escitalopram with other drugs are minimal, which is especially important for our proposed study, since these cardiac patients are likely to be on multiple cardiac medications. Compared with other anxiolytic medications, escitalopram is generally better tolerated, its onset of action is relatively fast, it requires no dose adjustment in renal dysfunction and older age, and its use may have cost–effective and cost–utility advantages. Therefore, we believe that escitalopram is the optimal choice as a safe and effective first-line option in the management of patients with high anxiety and with anxiety disorders. It should be noted that we also considered other medications, including different classes of medications for which anxiety is an indication (e.g., benzodiazepines), but rejected the use of medications such as diazepam because of potential adverse side effects (e.g., falls, cognitive impairment) and because such medications are addictive and promote drug dependence. Because of the relatively short (i.e., 12-weeks) intervention, patients randomized to placebo will have limited exposure to a “treatment” that may have minimal benefit. Moreover, only 30 patients (20%) will actually receive the placebo pill. The fact that 80% of patients will receive an active treatment (exercise or escitalopram) should also facilitate patient recruitment into the trial.

The value of treating subclinical anxiety disorders with SSRIs also was carefully considered by our research team. In view of the growing evidence that elevated anxiety, and not simply the diagnosis of an anxiety disorder, is associated with impaired quality of life and increased CHD risk,[11, 12, 163] we believe that treating cardiac patients with elevated symptoms of anxiety is justified. Escitalopram is considered the first line of psychotropic medications for treating elevated anxiety symptoms and not just for treating an anxiety disorder, and it is regarded as one of the safest and most widely prescribed anxiolytic medications in the US. The risks of receiving escitalopram include common side effects such as nausea, insomnia, headache, tremor, diarrhea, nervousness, dry mouth, increased sweating, and sexual dysfunction. Less common side effects include rash, bruising, agitation, and hyponatremia. We are also aware of recent FDA alerts regarding the possibility of SSRIs being associated with worsening of suicidal ideation, agitation, and depression, and we plan to include these warnings in the informed consent, and all patients will be counseled by the study psychiatrist about these potential risks. Importantly, we will exclude patients with a primary diagnosis of MDD, with active suicidal ideation, or who are judged to not be appropriate candidates for escitalopram or placebo therapy (e.g., prior non-responders, psychotic depression, active suicidal ideation, severe agitation, etc.). If such adverse events should develop during the course of the study, we will refer them for appropriate care immediately. We estimate that less than 10% of the patients may drop out due to such side effects.

11. Costs to the Subject: Subjects will not incur any costs related to study-related assessments or interventions.

12. Data Management and Statistical Considerations

Data Analytic Approach. The basic analytic strategy is a linear model carried out in the MPlus modeling software,[164] with treatment group contrasts as factors, and ethnicity, age, gender, and pre-treatment measure of the outcome variable as the adjustment covariables. The intent-to-treat principle (ITT) will be followed in all models, using full information maximum likelihood available in MPlus to manage missing data. For the case of the primary outcome, HADS-A, the model will include post-treatment HADS-A score as the response, with the predictors including two planned contrast variables representing 1) the two active treatments (exercise and escitalopram) vs. placebo and 2) exercise vs. escitalopram, with ethnicity, gender, age, and pre-treatment level of the HADS-A as the adjustment covariables. The contrast tests among treatment groups will be examined directly, i.e., no omnibus or "gateway" test will be required before interpreting them. In support of the HADS-A outcome, we also will compare the pattern of weekly changes in the STAI scores over time using a repeated measures model with Proc Mixed in SAS (SAS Institute, Cary, NC). The primary biomarker outcome, HRV, will be evaluated similarly. It is possible that a small number of participants may require off-protocol psychotropic medication during the course of the trial. These participants will be included in the ITT analysis and will not be replaced. We also will perform a sensitivity analysis with change in medication included as an adjustment variable in the statistical model. Finally, we will compare the treatments on the number of clinical events using a generalized linear model with the appropriate distributional form (e.g., negative binomial), using the same contrasts and covariates as in the linear model described above.

We also will examine treatment effects for a number of additional supportive outcome measures (e.g., BDI-II, QoL, inflammatory markers, BRS, urinary catecholamines, etc.). Significant treatment effects for these variables will help us interpret our primary outcomes and may inform further study and clinical application. For example, if the additional quality of life variables or CHD biomarker measures are also responsive to exercise treatment, it may indicate that exercise has a more global salutary effect above and beyond reducing anxiety. Despite their importance, we recognize that conducting these additional comparisons raises the potential for an inflated Type I error rate. We will therefore note in publications that these additional analyses represent exploratory analyses. We shall otherwise carry these analyses out using the same modeling approach as we do for the primary treatment analyses, attending in particular to the distribution of the residuals for each model and modifying our approach accordingly. The above models can be easily extended to include the 6-month follow-up measurement occasion.

Prior to conducting these analyses, preliminary examination of the assumptions of the model will be conducted to examine the homogeneity of regression assumption. This assumption requires that the relationship between treatment and the response variable be homogeneous for each level of the adjustment covariables. Should the data indicate that this assumption is violated, we will model the corresponding multiplicative (interaction) term(s). In addition to assessing the adequacy of the model with respect to the homogeneity of slopes assumption, we also will evaluate the model for violations of heteroscedasticity of errors and non-linearity using standard graphical methods. Should these assumptions be violated, appropriate transformations (e.g., Box-Cox method) will be made. All analyses of treatment effects for secondary hypotheses concerning continuous or binary variables will be conducted using the modeling capabilities available in MPlus.

In addition to treatment effects, we also will test the hypothesis that pre- to post-treatment change in HADS-A scores will mediate the improvements in intermediate CHD biomarkers. M-Plus allows a direct, formal test of this hypothesis via path analysis modeling. For example, a model will be specified so that both active treatment groups will be contrasted against the placebo arm, with a variable representing the change in anxiety intervening between the treatment contrast variables and post-treatment HRV (with the covariates, pre-treatment HRV, age, ethnicity, and gender). Mediation is tested by examining the product of the two component path coefficients (treatment ->mediator->outcome) and its standard error, which yields the point estimate of the mediated effect along with the statistical significance of treatment on post-treatment biomarker (e.g., HRV) via change in HADS-A.[165] We also will explore possible treatment-specific mediators (e.g., change in VO_2 mediating change in HRV for the Exercise group). In addition to the above tests, we will examine the impact of dropout on the estimates

of treatment effects using mixture modeling available in MPlus. Specifically, we will examine the primary outcomes using Rubin's Complier-Average Causal Effect Estimation (CACE) model,[166] which estimates the effect of treatment for all participants who adhere to the protocol irrespective of treatment group assignment. We will explore possible moderators of the treatment effect using interaction terms. Specifically, we will examine the possible moderating effects of gender, race, patient expectations, and initial severity of anxiety (e.g., DSM-5 diagnosis for an anxiety disorder); if sufficient numbers, we also plan to explore individual diagnoses by adding treatment interaction terms for these variables simultaneously with the primary model, and using a pooled test of the terms to determine whether the individual terms should be interpreted. Participants who voluntarily drop out of treatment or who are unable to complete our protocol will not be replaced but will undergo follow-up assessment.

Power Analysis. Our study is powered with a focus on the primary hypothesis test: the treatment effect on anxiety as measured by HADS-A scores. We estimated power and sample size under the following assumptions: an alpha of .05, a linear model with age, gender, ethnicity, and baseline HADS-A score as covariates, a conservative estimate of the R-squared of .20 for the full model predicting post-treatment HADS-A, a 15% attrition rate, and two planned contrasts: active treatment vs. placebo and exercise vs. escitalopram. The comparison of primary interest will be active treatments vs. placebo. We estimate that a sample size of 150 (127 after attrition) will yield .80 power to detect at least a .45 SD difference between the active treatments and Placebo. In the general linear model, the exercise vs. escitalopram test will be only slightly less powered in being able to detect a .50 SD difference. In response to a previous reviewer comment, we believe that achieving this effect size is feasible. For example, in individuals with high anxiety sensitivity, Broman-Fulks[167] reported a .61 SD difference between exercisers and controls. We also re-examined data from a subset of highly anxious patients (STAI≥45; N=32) participating in our recently completed UPBEAT study[49] and found an effect size of .85 SDs on the STAI for both active treatments vs. placebo controls. We note that our power estimates are conservative in that the R-squared for the model is likely to be greater than .20 and dropout may be lower than 15%. With respect to the secondary outcome of HRV, our prior work showed that the R-squared between the baseline covariates and HRV was .73, greatly increasing the power of the tests of treatment on HRV. For the test of exercise vs. escitalopram on HRV, our primary CHD biomarker of interest, we will have a power of .80 to detect a .25 SD effect at alpha of .05. Finally, for our ancillary outcomes, including FMD, lipids, urinary catecholamines, and inflammatory markers, we have sufficient pilot data for FMD, which we use as an exemplar for power estimates: our earlier work showed that for FMD, the multiple R-squared between the baseline covariates (age, gender, ethnicity, and baseline FMD) and FMD was .50. Thus, we will have a power of .80 to detect a .34 SD effect for FMD with an alpha of .05. We estimate the power for the secondary analysis of treatment on time-to-clinical-event, assuming an event rate of 50% in the placebo group (based on unpublished data from our prior work[49]), 42 months for patient accrual, median follow-up time of 30 months and alpha =.05, is .80 to detect a reduction in event rate of 50% between both treatment groups and placebo, as well as .80 to detect a reduction in event rate of 56% between either intervention group individually and placebo. Unpublished data from our recently completed ENHANCED trial[168] revealed a 54% reduction in major adverse cardiac events among patients participating in CR compared to a matched control group of patients who did not participate in exercise-based CR.

13. Data and Safety Monitoring: Study participants will be closely monitored for side effects, level of anxiety, and suicide risk. All patients will receive a weekly phone call to assess their state of anxiety using the STAI-State instrument. For patients who have a secondary diagnosis of MDD, BDI-II item #9 will be administered along with the 20-item STAI; patients who score >1 on the item #9 of the BDI-II or who are judged to be at increased risk for suicidality will be evaluated by our study psychiatrist and referred for further treatment. For patients with a secondary diagnosis of MDD, suicidality will be assessed at each visit and by interim telephone contacts as needed. Subjects may experience no response to treatment or a worsening of symptoms; however, all subjects will be carefully monitored and withdrawn from the study if their symptoms worsen. If patients become suicidal, they will be evaluated by the treating psychiatrist

and appropriate referral or admission procedures will be initiated, such as to their referring physician or to the Duke Outpatient Affective Disorders Program, the Duke Psychology Clinic, or a local mental health center. Our study coordinator will contact the patient within 24 hours to make sure that he or she followed through with the referral. Furthermore, at the conclusion of the interventions, patients will be followed bimonthly via telephone and referred to their local physicians for further treatment, if necessary, or to the Outpatient Treatment Program at Duke University Medical Center or to the Duke Psychology Clinic.

The Duke University Psychiatry Outpatient Clinic is staffed by Duke psychiatrists and psychologists who treat varying levels of severity of anxiety. The Duke University Psychology Clinic is staffed by the Duke clinical psychology faculty, postdoctoral fellows trained specifically in the treatment of anxiety disorders, and advanced clinical graduate students who see patients on a sliding fee schedule and who function under the supervision of licensed psychologists. We believe that these facilities, in addition to private practitioners in the community, can serve as appropriate referral sources for patients needing further treatment. We believe that careful monitoring of all patients entered into our protocol and tracking of all participants following the completion of the interventions will minimize risk to study participants. The study personnel, including physicians, psychologists, the study coordinator, and the physician's assistant, have the training and experience to provide the necessary safeguards for participation.

The study clinicians all have extensive experience in the treatment of anxiety disorders. The study psychiatrist (Dr. Wei Jiang) has served as a PI or co-PI on a number of clinical trials including many patients with CHD (e.g., REMIT, SADHART, MIIT, SADHART-CHF). Finally, we will organize a Data Safety and Monitoring Board consisting of a cardiologist (Dr. David Sheps, University of Florida), psychiatrist (Dr. Leo Pozuelo, Cleveland Clinic), and biostatistician (Dr. Diane Catellier, RTI).

At screening, if a patient is excluded on the basis of his or her suicide risk, study staff will contact the study psychiatrist (Wei Jiang, MD) and the study PI (James Blumenthal, PhD) to develop an appropriate safety plan, including referral for psychiatric care. The participant’s primary care physician, with patient consent and approval, also will be notified. Also at screening, patients will be informed of the potential side effects of SSRIs and the risks/benefits. Participants are required to inform the research team of any medication changes as prescribed by their medical providers.

Management of Worsening Depression or Active Suicidal Ideation: In addition to weekly assessments, participants are advised to contact the study team should they believe their symptoms become worse or they develop active suicidal ideation. An interim visit or phone contact with Dr. Jiang may be required. Patients who report suicidal ideation will be immediately evaluated by Dr. Jiang, the study psychiatrist. Patients who present with acute and active suicidal ideation will be terminated from the study and referred for further psychiatric care as needed.

14. Privacy, Data Storage, and Confidentiality: All participant data will be kept in locked offices and electronic data in password-protected folders on the shared drive that are only accessible to key personnel.

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