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Enhancing Standard Cardiac Rehabilitation with Stress Management Training: Background, Methods, and Design for the ENHANCED study

James A. Blumenthal, PhD[1], **Jenny T. Wang, PhD**[1], **Michael Babyak, PhD**[1], **Lana Watkins, PhD**[1], **William Kraus, MD**[2], **Paula Miller, MD**[3], **Alan Hinderliter, MD**[3], and **Andrew Sherwood, PhD**[1]

[1]Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC

[2]Department of Medicine, Duke University Medical Center, Durham, NC

[3]Department of Medicine, University of North Carolina – Chapel Hill, Chapel Hill, NC

Abstract

PURPOSE: Enhancing Standard Cardiac Rehabilitation with Stress Management Training in Patients with Heart Disease (ENHANCED) is a randomized clinical trial (RCT) funded by the NHLBI to evaluate the effects of stress management training (SMT) on changes in biomarkers of risk and quality of life for patients enrolled in traditional exercise-based cardiac rehabilitation (CR).

METHODS: One hundred fifty cardiac patients recruited from Duke University and the University of North Carolina will be evaluated and randomized to CR enhanced by SMT (including sessions devoted to relaxation training, cognitive restructuring, communication skills, and problem solving) or to standard exercise-based CR. Before and following 12 weeks of treatment, patients will undergo a battery of psychometric questionnaires and evaluation of cardiovascular biomarkers including measures of flow-mediated dilation, heart rate variability, baroreflex sensitivity, platelet function and inflammation, and ischemia during laboratory mental stress testing. The primary outcomes include a composite measure of stress (distress, depression, anxiety, and hostility and 24-hr urinary catecholamines and cortisol) and a composite measure of cardiac biomarkers of risk (vascular endothelial function, cardiac vagal control, inflammation, platelet function and mental stress-induced myocardial ischemia). Secondary outcomes include measures of quality of life as well as clinical events including death, hospitalizations, myocardial infarction, and revascularization procedures.

RESULTS: This article reviews prior studies in the area and describes the design of the ENHANCED study. Several key methodological issues are discussed including the assessment of biomarkers of risk and barriers to the integration of SMT into traditional CR.

Corresponding Author: James A. Blumenthal, PhD Box 3119 Department of Psychiatry and Behavioral Sciences Duke University Medical Center, Durham, NC 27710 Tel: (919)-684-3828; Fax: (919) 684-8629; Blume003@mc.duke.edu.

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CONCLUSIONS: The ENHANCED study will provide important information by determining the extent to which SMT combined with exercise-based CR may improve prognosis and quality of life in vulnerable cardiac patients.

Keywords

Cardiac rehabilitation; stress; biomarkers; depression; heart rate variability

Coronary heart disease (CHD) is the leading cause of death in the United States, affecting 1 million people each year. In 2004, 871,500 people died of CHD, accounting for 36% of all U.S. deaths.[1] We now know that traditional risk factors (eg, cigarette smoking, hyperlipidemia, diabetes, hypertension) do not fully account for the timing and occurrence of CHD events, and it is widely recognized that stress and negative emotions affect the development and course of CHD.[2-4] For example, in the INTERHEART study, a composite "stress" index score was shown to have an odds ratio of 2.67 adjusted for all other risk factors, which was comparable to the "traditional" risk factors.[5-6] Psychological risk factors such as hostility have been shown to predispose individuals to the occurrence of myocardial ischemia[7] and anger has been shown to be a trigger for acute myocardial infarction (MI)[8-9] and myocardial ischemia.[10] There is even stronger evidence that clinical depression is associated with increased risk for fatal and non-fatal CHD events among both healthy persons and cardiac patients.[11] Meta-analytic studies have suggested that depressive symptoms are associated with a mortality odds ratio of 2.24.[12] Importantly, even depressive symptoms that do not meet formal DSM-IV criteria for MDD have been associated with increased risk among CHD patients.[13] Other studies have shown that acute stress from major catastrophic events such as war[14] and earthquakes,[15] as well as stress at work,[16] chronic anxiety and panic attacks[17-19] can also trigger CHD events.

This evidence has also provided the rationale for developing interventional strategies to reduce stress in susceptible individuals in order to modify the natural history of these clinical events. Indeed, there are now promising data to suggest that stress management training (SMT) is one such approach, and that SMT can have beneficial effects on psychosocial and medical outcomes.[3] However, many of the randomized clinical trials (RCTs) employing stress management approaches in CHD patients have had important methodological limitations and several of the larger RCTs have failed to demonstrate a benefit for SMT over usual care,[20-21] raising questions about the value of SMT for patients with CHD. Moreover, selecting appropriate endpoints for SMT interventions has proven to be highly challenging for clinical investigators. Reliance on "hard" clinical endpoints is problematic because studies require such large sample sizes that they are logistically difficult to conduct and are prohibitively expensive. The use of intermediate pathophysiologic endpoints that have been shown to be independently associated with increased risk represents a novel and exciting opportunity to study the benefits of SMT on meaningful biomedical outcomes that could provide a basis for larger RCTs. The ENHANCED study was developed in response to a Program Announcement (PA-07-322) inviting proposals to assess the efficacy of stress management compared to usual care in improving intermediate outcomes relevant to mental stress influences on major cardiac events in patients with coronary heart disease (CHD). We believe that the context of cardiac rehabilitation (CR) is an ideal setting in which to examine this issue.

EXERCISE AND STRESS MANAGEMENT INTERVENTIONS IN CARDIAC REHABILITATION

Exercise-based Cardiac Rehabilitation

The US Public Health Service defines cardiac rehabilitation services as "comprehensive, long term programs involving medical evaluation, prescribed exercise, cardiac risk factor modification, education, and counseling".[22] Currently, exercise-based CR, involving 12-weeks/36 sessions of aerobic exercise supplemented with resistance training is the primary treatment for most CR programs in the United States.[23] Proper medical management is also emphasized, along with weight loss and nutrition, and smoking cessation.[24] Although no single study has demonstrated definitively that exercise reduces morbidity in patients with CHD, pooling data across clinical trials has shown that exercise may reduce risk of fatal CHD events by 25%.[22,25-26] The Clinical Practice Guidelines for Cardiac Rehabilitation[22] provided a comprehensive review of the literature and confirmed the value of exercise training in cardiac patients for improving a number of clinical endpoints, including survival. In contrast, the *Health Care Bulletin on Cardiac Rehabilitation*[27] concluded that "exercise improves physical aspects of recovery at no additional risk, but as a sole intervention it is not sufficient to reduce risk factors, morbidity, or mortality." These conclusions are different from prior reviews[25-26] that suggested that there was no difference in outcomes comparing exercise alone or in combination with other behavioral interventions. Because previous studies cited in the meta-analyses were small, methodologically flawed, and often limited to primarily low-risk, middle-aged post-MI men, with few women, minorities, or other cardiac patient groups the clinical value of exercise as a sole treatment for cardiac patients remains ambiguous. A recent, comprehensive meta-analysis by Jolliffe et al[28] reported a 27% reduction in all cause mortality for exercise only, but surprisingly only a 13% reduction for "comprehensive" CR. Cardiac mortality was reduced by 31% in the exercise only and 26% in comprehensive CR when compared to usual care. As a result, Jolliffe et al[28] concluded that exercise-based CR was effective in reducing cardiac deaths, but that it was unclear if exercise only or if a comprehensive CR program was more beneficial. As such, there is no consensus on whether traditional exercise-based CR is an effective "stand-alone" treatment for cardiac problems.

Stress Management Training in CHD Patients

It is widely believed that psychosocial interventions can benefit patients with CHD.[4, 29-31] Studies have shown that psychosocial interventions are associated with reduced rates of rehospitalization,[32] cardiac death,[33] total cardiac events,[31] and improved risk factor modification.[32,34] In a partially randomized trial, Friedman et al[35] reported that the nonfatal reinfarction rate was 12.9% among the 592 patients receiving Type A modification compared to 21.2% among 270 controls who only received cardiologic counseling after 4.5 years. Several reviews have provided very optimistic assessments of the value of SMT in cardiac patients. For example, Linden et al[29] compared 2024 patients who received psychosocial interventions and 1156 control subjects who received standard medical therapy and usually some form of exercise training. Relative to controls, psychosocially treated patients showed greater reductions in psychological distress, but also in lower blood pressure, heart rate, and cholesterol levels. Patients who received psychosocial interventions were over 40% less likely to die and were 65% less likely to have a recurrent coronary event than controls over a 2 year follow-up period. In a recent review, Rees et al[20] aggregated findings from 18 studies in which 5242 patients were randomized. Although there was limited support for the benefits of stress management on total mortality in the 10 trials that reported death as an outcome (OR = 0.9; 95%CI 0.7-1.2) and on cardiac mortality in 4 studies (OR = 0.6; 95%CI 0.4-0.99), there was evidence of a significant reduction in nonfatal MI compared to controls (OR = 0.7; 95%CI 0.5-0.9) in 8 studies.

To date, we are not aware of any RCTs that have evaluated the added benefit of combining traditional exercise-based CR and SMT. A prior study conducted at Duke found that SMT reduced the occurrence of myocardial ischemia in the laboratory and during daily life and was also associated with better clinical outcomes compared to usual care.[36-37] Compared to the usual care group, the relative risk of an event after adjusting for baseline risk factors was 0.26 for the SMT group and 0.68 for the exercise group. Thus, the SMT intervention not only modified psychological outcomes, but also had a significant impact on longer-term clinical outcomes.[36] Moreover, a subsequent 5-year follow-up revealed that patients who underwent stress management continued to exhibit improved clinical outcomes over the follow-up period compared to both the exercise training and usual medical care control groups and had lower health care costs compared to the other groups.[37] However, these results were considered inconclusive because the usual care control patients were not randomized.

We conducted a subsequent study that employed a fully randomized design including a usual care control group, but exercise and SMT were delivered separately.[38] Patients in both active treatment groups exhibited reductions in depression and distress compared to usual care controls. Patients in both active treatment groups also exhibited smaller reductions in left ventricular ejection fraction during mental stress testing, and greater improvements in a variety of cardiovascular “biomarkers” including flow mediated dilation and baroreflex sensitivity. Interestingly, SMT patients also exhibited greater improvements in heart rate variability compared to exercisers and usual care controls, suggesting the potential added value of combining SMT with exercise training in CHD patients. While the benefits of SMT were confirmed, the design did not address the question of the *added value* of combining SMT with exercise. This issue is critically important because while exercise is a critical component of most CR programs, it is not known if SMT can add to the benefits of traditional exercise-based CR. Currently, SMT in cardiac rehabilitation programs provide education about the importance of stress and relaxation techniques; however, more intensive techniques such as problem-solving and cognitive restructuring are not typically provided or integrated into daily life.

Another important methodological challenge in evaluating the usefulness of SMT has been selecting appropriate endpoints for SMT interventions. The use of intermediate pathophysiologic endpoints shown to be independently associated with increased cardiac risk provides an innovative way to evaluate the benefits of SMT on meaningful biomedical outcomes for vulnerable cardiac patients. Thus, we believe that a randomized control trial is warranted to (1) assess the extent to which combining exercise-based CR and SMT is more effective at improving biomarkers in vulnerable CHD patients compared to CR alone and (2) to test the hypothesis that reductions in stress will mediate the relationship between SMT and improvements in biomarkers.

METHODS

The Enhancing Standard Cardiac Rehabilitation with Stress Management Training in Patients with Heart Disease (ENHANCED) study is an RCT in which 150 men and women with CHD will be randomly assigned to 1 of 2 conditions: 1) exercise-based CR or 2) SMT-enhanced exercise-based CR. Participants will undergo assessments of cardiovascular biomarkers at baseline and complete psychosocial assessments, which will be repeated after completion of the 12-week intervention. Randomization of patients will proceed using a conditionally random assignment plan, with assignment conditional upon gender, age (<60 or ≥ 60), stress level (General Health Questionnaire [GHQ] <5 or ≥ 5), and left ventricular ejection fraction (LVEF) (<40% or ≥ 40%). Our protocol was approved by the National

Institutes of Health and by the Institutional Review Boards at Duke University and the University of North Carolina.

Participant Eligibility

The ENHANCED study will involve patients recruited at Duke University and University of North Carolina – Chapel Hill (UNC). Sample size was chosen to ensure adequate power to compare the effects of SMT-enhanced CR versus standard CR on our primary (ie, intermediate biomarkers of cardiovascular risk and measures of stress) and secondary endpoints (ie, death or first cardiac-related hospitalization). We plan to recruit 35% female and 25% minority patients for this study to improve upon the generalizability of previous studies. Male or female outpatients ≥35 years of age with a documented history of CHD who are eligible for cardiac rehabilitation in North Carolina, have capacity to provide informed consent and follow study procedures will be included in the study. Patients who have received a heart transplant or valvular repair, LVEF < 30%, labile ECG changes prior to testing, current use of a pacemaker, resting BP >200/120mm Hg, left main disease >50%, or are unable or unwilling to comply with assessment procedures or to be randomized into treatment groups will be excluded.

Interventions

Standard cardiac rehabilitation—The CR programs at Duke and UNC, like most programs in US, are primarily exercised-based with modest attention to nutritional factors, medication adherence, and psychosocial issues. Patients exercise 3 times a week for 3 months at a level of 70-85% of their initial peak heart rate reserve or at their maximum heart rate without pain, or ST-segment depression >2 mm, as determined at the time of their initial exercise treadmill test. Exercise consists of 10 minutes of warm-up exercises followed by 30-35 minutes of continuous walking, biking, or jogging under medical supervision. Patients also receive several classes in nutrition based upon the standard American Heart Association (AHA) guidelines[39] and 2 classes devoted to the role of stress in heart disease. Stress management training is not provided to most patients, and while a few patients may be referred for more intensive treatment (<5%), even fewer patients actually receive mental health services.

SMT-enhanced cardiac rehabilitation: Combining standard CR and SMT—Patients in this condition will receive the identical standard CR intervention *plus* SMT. SMT is based upon our previous intervention studies[36,38] that use a cognitive-social learning model of behavior and successfully reduced ischemic activity and improved psychological functioning. The intervention is delivered in a group, and focuses on the dynamic interaction of the social environment with personality traits that predispose the individual to respond in particular ways. There will be twelve 1.5-hour sessions in the treatment module. Treatment methods include lectures, demonstrations, readings, and weekly assignments of behavioral drills between sessions.

Ongoing medical care—All patients, including those in the SMT condition, will receive CR and will continue with their regular medical care. This care includes the provision of educational information about CHD and its treatment. All patients will be followed by their cardiologists who, in an ongoing fashion, will manage any episodes of escalating symptoms or disease progression.

Assessments

Patients will be assessed at baseline and after 3 months of treatment. Psychosocial measurements of stress will include self-report questionnaires of somatic symptoms, health

behaviors, physical activity, depression, anxiety, hostility, social support, quality of life, coping, and quality of marriage. Physiological biomarkers will assess for cardiovascular risk factors in each patient.

Measures of Stress and Health Behaviors—In order to assess stress levels and relevant health behaviors, participants will complete a battery of psychometric tests including the (GHQ),[40] the Beck Depression Inventory (BDI),[41] the state and trait anxiety versions of the State-Trait Anxiety Inventory (STAI),[42] and the Cook-Medley Hostility (Ho) Scale.[43] We also will assess medication adherence using the Brief Medication Questionnaire,[44] dietary habits using a 7-day retrospective food frequency questionnaire,[45] and physical activity using the CHAMPS Activities Questionnaire.[46] Because SMT consists of a number of components (eg, progressive muscle relaxation, coping skills training, communication skills, problem solving, etc.), we also will examine the ingredients of SMT in order to document the effectiveness of the SMT intervention and provide insights into the active components of SMT that could be responsible for observed improvements in the outcomes. For example, because improved coping is believed to be one mechanism responsible for reduced distress, we will be evaluating coping strategies using the Brief Cope questionnaire[47] and we also will administer the Dysfunctional Attitudes Scale[48] to provide an additional indicator of participant use of negative cognitive processing in approaching life problems. We also will assess social support with the Perceived Social Support Scale (PSSS).[49]

Cardiovascular Biomarkers of Risk

Flow-mediated dilation (FMD): Assessment of endothelial function—Our technique for assessing flow-mediated dilation (FMD) follows procedures first described by Celermajer et al[50] and conforms to current standards established by committee guidelines published in 2002.[51] Longitudinal B-mode ultrasound images of the brachial artery will be acquired using a high-frequency transducer at baseline and during reactive hyperemia induced by 5 minutes of forearm occlusion. FMD will be calculated as the maximum percent change in arterial diameter relative to pre-inflation baseline.

Baroreceptor reflex sensitivity (BRS) and heart rate variability (HRV): Indices of cardiac vagal control—A Finapres noninvasive blood pressure monitor (Ohmeda, Madison, WI) will be used for beat-to-beat blood pressure assessment.[51] During the last 10 minutes of a 20 minute resting period, continuous beat-to-beat blood pressure and R-R interval measurements will be recorded for noninvasive assessment of BRS and HRV.

Measures of platelet activation, chronic inflammation, and stress hormones—Morning blood samples will be obtained for measurement of platelet activation and aggregability, and biomarkers of inflammation. Participants also will collect 24-hour urine specimens for measurements of norepinephrine, epinephrine, and free cortisol excretion.

Physiological responses to mental stress—Laboratory stressors have been shown to elicit episodes of transient myocardial ischemia in susceptible individuals,[53-54] and stress-induced ischemia is associated with an increased risk of adverse events.[55-58] Participants will undergo a standardized laboratory mental stress procedure with simultaneous echocardiographic monitoring for ischemia. The stressor will consist of preparation and delivery of a speech about a current events topic. During the speech, standard 2-dimentional ultrasound images of the left ventricle will be acquired for subsequent off-line analysis by an experienced echocardiographer who is blinded to treatment group and other patient data. Regional left ventricular wall motion will be assessed using a 16-segment model.[59] The motion of each segment will be graded on a scale from 0 to 3 and a wall motion score index

(WMSI) will be calculated as the sum of scores divided by the number of segments visualized as described by Gottdiener et al.[60]

Statistical Analysis

Treatment effect on primary outcomes—The initial test will be of the treatment effects on the primary endpoints: stress and biomarkers of cardiovascular risk. For this analysis we will use the procedure for multiple endpoints recommended by O'Brien[61] and follow the intent to treat principle. We will create separate global scores for the stress (general distress (GHQ), depression (BDI), anxiety (STAI), anger (Ho), and 24-hour urinary epinephrine and cortisol) and biomarker measures (FMD, BRS, CRP, LTA, and mental stress-induced myocardial ischemia). We also will explore the extent to which the treatment might be differentially effective across subpopulations, including levels of resting LVEF, age, medications, treatment site, gender, ethnicity, and pretreatment levels of stress.

Treatment effect on clinical outcomes—The Cox proportional hazards model will be used to evaluate the effect of treatment on the composite endpoint of death or first cardiac-related hospitalization. Patients who have not experienced an event before the follow-up period has ended will be coded as censored at the time of last-contact. In addition to examining standard regression assumptions, assumptions specific to the Cox model will be assessed using techniques suggested by Shoenfeld.[62] We will use Harrell's Design and Hmisc libraries[63] in the R software package (http://cran.r project.org) to conduct these analyses. As was the case for the analysis of stress variables and risk biomarkers, we also will add propensity adjustment to this analysis, and also will explore the extent to which the treatment might be differentially effective across subpopulations using a series of models that include treatment by subgroup interaction terms.

Analysis of mediators—The general approach to the statistical test of mediation is as follows. We will evaluate a) the extent to which the stress variables mediate the relation between treatment and risk biomarkers, and b) the mediating role that risk biomarkers and the stress variables have between treatment and clinical event outcomes. These analyses proceed by establishing first that a) the treatment has a meaningful effect on the outcome of interest; b) the treatment is related to the mediator; and c) the mediator is related to the outcome. In a final step, the mediator and treatment indicator are included simultaneously as predictors of the outcome of interest.

CONCLUSIONS

To date, previous studies employing stress management approaches in CHD patients have had important methodological limitations and several of the larger RCTs have failed to demonstrate a benefit for SMT over usual care.[22,37] These limitations have raised questions about the value of SMT for patients with CHD. The selection of appropriate endpoints for SMT continues to be a challenge as “hard” clinical endpoints require large sample sizes that are burdensome to conduct and expensive. The use of intermediate pathophysiologic endpoints presents a unique way to study the benefits of SMT on meaningful biomedical outcomes that have been shown to be independently associated with increased risk and could provide a basis for larger RCTs. The ENHANCED study will begin patient recruitment in January 2010 and is scheduled to conclude enrollment in May 2014.

CONDENSED ABSTRACT

Enhancing Standard Cardiac Rehabilitation with Stress Management Training in Patients with Heart Disease (ENHANCED) is a randomized clinical trial examining the added value of stress management training (SMT) in the context of cardiac rehabilitation (CR).

Participants undergo evaluations of stress and cardiovascular biomarkers. Results have implications for including SMT within standard CR.

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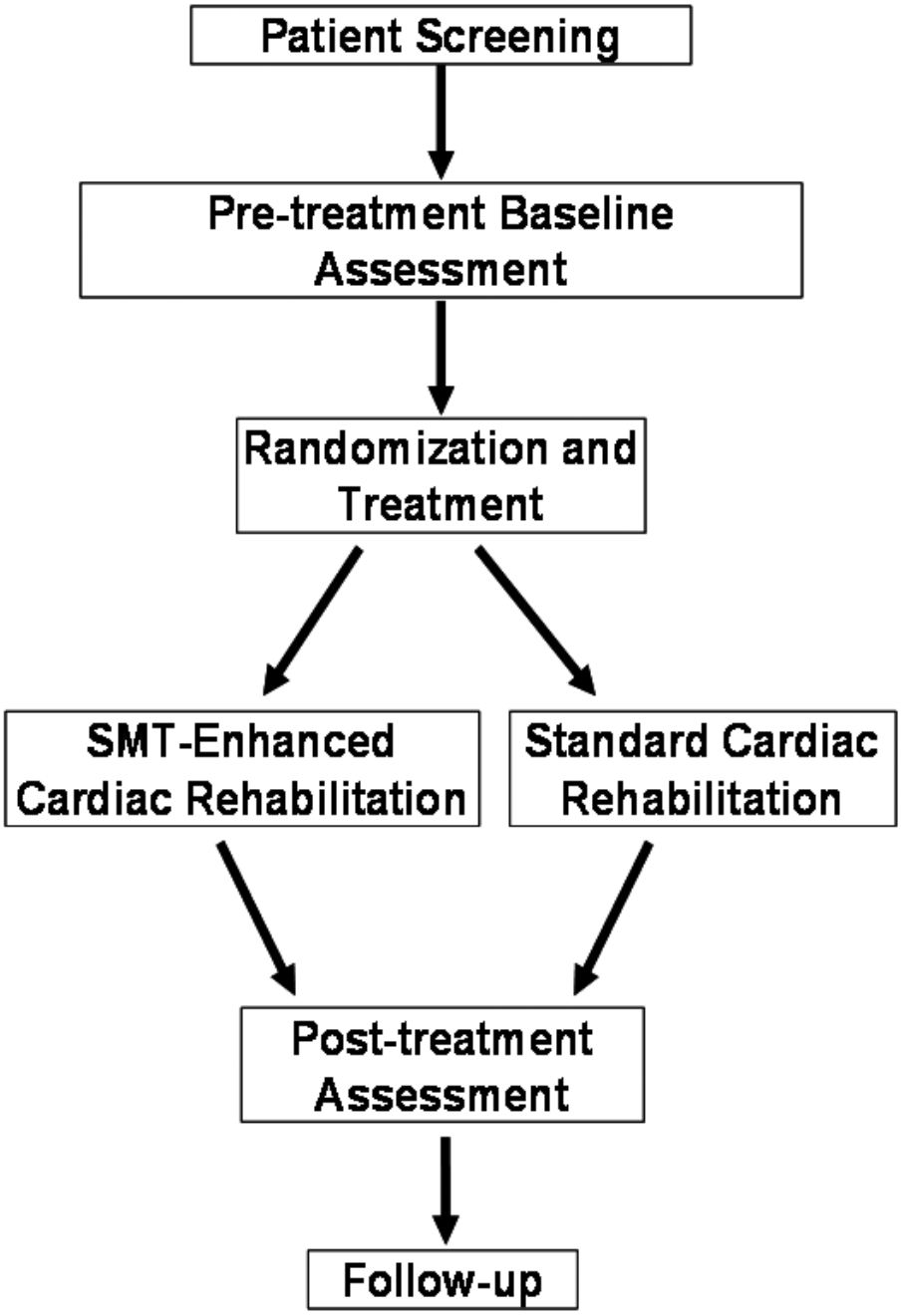

Figure 1.

The proposed investigation involves (1) a careful screening of potential participants; (2) a thorough pre-treatment assessment of stress and biomarkers of risk; (3) a randomized clinical trial of cardiac rehabilitation alone and *Stress Management Trteatment (SMT)-enhanced* cardiac rehabilitation; (4) post-treatment assessment of the impact of the 3-month intervention on cardiovascular biomarkers and quality of life; and (5) follow-up in which we plan to follow all participants for at least 6 months and up to 4 years (median 30 months) to assess clinical events including myocardial infarction, death, and cardiac-related hospitalizations.

TABLE 1

MEASURES OF STRESS AND HEALTH BEHAVIORS

General Health Questionnaire[40]	A 34-item self-report measure that assesses patient perceptions of health, well-being, and ability to perform daily activities.
Beck Depression Inventory[41]	A 21-item self-report inventory of depression that has been shown to be predictive of clinical events in coronary heart disease patients.
State-Trait Anxiety Inventory[42]	An anxiety measure consisting of 2 separate self-report inventories, 1 measuring state anxiety, and the other trait anxiety.
Cook-Medley Hostility Scale[43]	A 50-item true or false questionnaire derived from the Minnesota Multiphasic Personality Inventory that measures cynical hostility.
Brief Medication Questionnaire[44]	Patients reconstruct their medication regimen over the past 7 days, including the names of medications, dosages, indications, and self-report of missed doses; also asks several questions about barriers to adherence such as memory difficulty or side effects.
7-day retrospective Food Frequency Questionnaire[45]	Patients are asked to recall typical consumption of various food groups over a 1 week period.
CHAMPS Activities Questionnaire[46]	A comprehensive self-report measure of exercise activity for use among sedentary older adults.
Brief Cope Questionnaire[47]	An instrument assessing the use of coping strategies for use among healthy adults as well as adults with chronic illness.
Dysfunctional Attitudes Scale[48]	An additional indicator of participant use of negative cognitive processing in approaching life problems.
Perceived Social Support Scale[49]	A measure assessing perceived levels of social support.