Title: Targeting Obesity to Optimize Health in Cardiac Rehab (TOPCARE)
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Study Title: Targeting Obesity to Optimize Health in Cardiac Rehab (TOPCARE)

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Background, Rationale and Context

Coronary heart disease (CHD) affects more than 15 million US adults and is a primary cause of morbidity and mortality.[1] Although CHD treatment guidelines recognize obesity as a major modifiable risk factor,[2] **nearly half of all CHD patients are obese** and the current standard of care fails to implement evidence-based obesity treatment for this high-risk population.[3-5] This presents a critical opportunity to address an unmet need and identify more effective approaches that benefit not only survival but also health status.[6]

Cardiac rehabilitation programs are integral in the treatment of CHD and significantly reduce hospital readmissions and mortality.[7,8] Yet, **the efficacy of exercise-based cardiac rehabilitation for improving exercise capacity and CHD risk factors is markedly blunted in CHD patients with obesity**.[9-12] Current programs largely focus on nutrient intake and produce minimal weight loss, on average <3%.[13,14] Our data show that despite appropriate exercise prescription and adherence, only 22% of CHD patients with obesity lose even the minimum recommended body weight (≥5%)[15] over a 3-month program. These findings indicate that targeting reductions in caloric intake is needed to optimize outcomes in these patients and suggest that current programs are too short to produce adequate weight loss and ensure the necessary behavioral adaptations for long-term maintenance.

Multiple lines of evidence suggest that **weight loss improves outcomes** in CHD patients. Observational data indicate that CHD patients who lose weight during cardiac rehabilitation have the greatest improvements in exercise capacity and CHD risk factors[10,11,16] and a lower risk of events and mortality.[16-18] Additionally, randomization to diet-induced weight loss in combination with aerobic exercise improves exercise capacity, quality of life, and CHD risk factors more than exercise alone[19-21] and reduces long-term mortality in overweight and obese adults.[22-24] We recently reported similar findings in heart failure patients.[25] Despite the available evidence that diet-induced weight loss is beneficial in adults with and without CHD, patients with index events <1-3 months prior have traditionally been excluded from weight loss studies. As such, the safety and efficacy of a calorie-restricted diet in the subacute period, when initiation of other medical and lifestyle therapies (including exercise-based cardiac rehabilitation) is critical, has not been adequately investigated. Furthermore, the effects of such interventions on the cerebral circulation remains largely unknown.

Objectives

The **primary goal** of this pilot study is to determine the feasibility of adding a 6-month behavioral weight loss intervention to exercise-based cardiac rehabilitation. Secondary goals are to examine the effects of the weight loss intervention on body weight, body composition (by DXA), exercise capacity (6-min walk distance), quality of life (SF-36), cardiac structure and function (by MRI), arterial stiffness, cardiometabolic risk factors (blood pressure, glucose, lipids), and biomarkers of cardiac injury (BNP, CRP, troponin I, troponin T, and cardiac-specific microRNAs). Tertiary goals are to explore the effects of the weight loss intervention on neurovascular outcomes (cerebral autoregulation, baroreflex sensitivity, and cerebral vasomotor reactivity). To accomplish these goals, we will randomize 40 overweight and obese adults (BMI ≥25 kg/m^2) aged ≥40 years with CHD to cardiac rehabilitation (Rehab) alone or to

cardiac rehabilitation plus a behavioral weight loss intervention (Rehab+WL). We will also assess each participant's readiness to change using the stages and processes of change for weight management (S-Weight and P-Weight)[26-28] in order to address the following **Specific Aims**:

- **Primary Aim:** To determine the feasibility of recruiting and retaining CHD patients with obesity in a 6-month behavioral weight loss intervention during cardiac rehabilitation
- **Secondary Aim:** To estimate the efficacy of a 6-month behavioral weight loss intervention on novel and traditional CHD risk factors during cardiac rehabilitation
- **Tertiary Aim:** To assess whether the level of motivation and readiness to change influence recruitment, retention, adherence, and CHD outcomes during cardiac rehabilitation
- **Exploratory Aim:** To explore the efficacy of a 6-month behavioral weight loss intervention on neurovascular outcomes

Methods and Measures

Study Overview

This study is a 2-arm, 6-month, randomized, clinical trial designed to determine the feasibility of adding a behavioral weight loss intervention to a standard exercise-based cardiac rehabilitation program. Secondary goals are to examine the effects of the weight loss intervention on body weight, body fat (by DXA), exercise capacity (6-min walk distance), quality of life (SF-36), cardiac structure and function (by MRI), arterial stiffness, cardiometabolic risk factors (blood pressure, glucose, insulin, lipids), and biomarkers of cardiac injury (BNP, CRP, troponin I, troponin T, and cardiac-specific microRNAs). In exploratory analyses, we will examine the effects of the weight loss intervention on cerebral autoregulation (CA), baroreflex sensitivity, (BRS), and cerebral vasomotor reactivity (CVMR). We will also assess each participant's readiness to change using the stages and processes of change for weight management (S-Weight and P-Weight) to evaluate their influence on recruitment, retention, adherence, CHD outcomes, and neurovascular outcomes. To accomplish these goals a total of 40 middle-aged and older men and women with obesity who are referred to cardiac rehabilitation at Wake Forest Baptist Hospital for CHD will be randomized to cardiac rehabilitation (Rehab) alone or to cardiac rehabilitation plus a weight loss intervention known to elicit weight and fat loss (Rehab+WL).

Selection Criteria for Study Participants

We will enroll 40 middle-aged and older men and post-menopausal women with CHD who are overweight or obese and/or have been referred to an outpatient cardiac rehabilitation program at a WFBH site including Wake Forest Baptist Medical Center (WFBMC), Davie Medical Center (DMC), and Lexington Medical Center (LMC). Patients who meet the following inclusion criteria will be asked to participate: 1) documented CHD defined as recent hospitalization for MI/heart attack, coronary artery bypass grafting (CABG), or percutaneous coronary intervention (i.e., angioplasty, stent); 2) age ≥40 years; and 3) overweight or obese based on an elevated BMI (≥25 kg/m^2). Major exclusion criteria include: body weight >450 lbs; congestive heart failure (ejection fraction <35%); advanced kidney disease (on dialysis or dialysis anticipated within 6 months); cognitive impairment (Montreal Cognitive Assessment [MoCA] score <22);[29] major depression (Patient Health Questionnaire [PHQ-9] ≥20);[30] severe pulmonary disease (i.e., oxygen-dependent); significant impairment from a prior stroke or other neurologic disease or injury; high risk for non-adherence (i.e., unwilling or unable to comply with study requirements); current participation in physical therapy or in another research study that prohibits co-enrollment; regular use of weight loss medications (e.g., orlistat); prior weight loss procedure (e.g., gastric bypass, sleeve gastrectomy, gastric banding); women who are pregnant or premenopausal (i.e., menses within past year); drug / substance abuse or excessive alcohol consumption (>14 drinks/week) within past 6 months; peanut allergy; and milk allergy/lactose intolerance.

Recruitment and Screening of Study Participants

To recruit CHD patients that are most clinically relevant and at the greatest risk of events, our main recruitment strategy will be to identify eligible participants from among the inpatient population at WFBH. We will work with specially-trained nurses serving as cardiac wellness coordinators and cardiac rehabilitation staff to ensure that potentially eligible patients are identified and contacted as soon as possible. Patients will be screened while in the hospital for the presence of CHD, for possible candidacy for cardiac rehabilitation, and to assess ability and willingness to participate in the research study . If interested, the study coordinator will contact the patient to review the inclusion and exclusion criteria and schedule the screening visit. This visit will take place on the same day as the cardiac rehabilitation consultation or on a separate day, if necessary. The standard cardiac rehabilitation consultation includes a thorough review of the patient's medical history; measurement of height, weight, waist circumference, and vitals; and assessment of dietary habits, health literacy, and quality of life. After obtaining informed consent, this information will be reviewed by the study coordinator, and patients will be asked to complete the MoCA to confirm eligibility. WFBH has a systematic referral process in place to help increase access to and enrollment in cardiac rehabilitation. Currently, 50-80 patients are referred to the WFBH cardiac rehabilitation program each month and 6-8 new patients start each week. Considering our primary inclusion criteria based on age, obesity, and CHD status, we expect to recruit 1-2 participants per week. Every effort will be made to enroll participants within 2 weeks of hospital discharge (i.e., 3 weeks after index CHD event), as early enrollment not only increases participation and completion rates, but also positively impacts body weight and exercise capacity.[31, 32] Additional strategies for recruitment may include targeted searches in electronic databases (e.g., based on relevant diagnostic and procedural codes). Recruitment personnel may also periodically visit the clinics of cardiology providers and work with a broad range of health professionals (e.g., medical fellows, physician assistants, nurse practitioners) to identify potentially eligible patients. An informational/invitational letter may be mailed to potential patients and followed up with telephone contact within 1-2 weeks.

Randomization

Patients who meet all inclusion/exclusion criteria and provide informed consent to participate will be randomized to Rehab only or Rehab+WL using a randomization scheme with blocking stratified by sex and obesity severity (BMI<30 vs. BMI≥30 kg/m^2). Block size and the randomization sequences will be unknown to all other study personnel. Study staff will be able to access individual treatment assignments through the study database which will be managed in the secure, web-based application REDCap (Research Electronic Data Capture).[33]

Study Interventions

Cardiac Rehabilitation

All participants will undergo standard exercise-based cardiac rehabilitation at a WFBH site which consists of three exercise sessions and one group health/nutrition education class per week for 12 weeks.[34] Participants also have one meeting with a dietitian, usually within the first 2 weeks of the program, to discuss dietary concerns and address issues noted in the dietary assessment. In order to provide sufficient time for adequate weight loss and ensure the necessary behavioral adaptations for long-term maintenance of lifestyle changes, all participants will undergo an additional 12 weeks of supervised cardiac rehabilitation for a total period of 6 months. Cardiac rehabilitation will be conducted by program staff (including exercise physiologists, nurses, and dietitians) with many years of experience in risk factor management and exercise prescription.

***Exercise**:* Each exercise session lasts for 60 to 90 minutes and consists of 5-10 minutes of warm-up and cool-down activity; up to 30 minutes of aerobic exercise using a variety of modalities (e.g., walking laps on a track, cycle ergometry, treadmills, stair climbers); and 15-20 minutes of upper and lower body resistance exercises using Thera-Bands. An exercise physiologist creates an individualized plan based on

patient history, comorbidities, orthopedic limitations, previous physical activity, and clinical status according to the American College of Sports Medicine Guidelines for Exercise Testing and Prescription.[35] Rating of Perceived Exertion (RPE) based on the Borg scale (range: 6-20)[36] will also be utilized to monitor exercise progression, with an RPE goal of 11-13 ("fairly light" to "somewhat hard") during the first week and an RPE goal of 12-15 ("somewhat hard" to "hard") by the end of the sixth week.[35, 37] Blood pressure and/or HR will be measured before and after each exercise session. During exercise HR and RPE will be used to monitor compliance to the prescribed exercise intensity.[38]

Health Education*:* Group education classes conducted by an exercise physiologist and/or dietitian are designed to provide support and general information on healthy lifestyle behaviors. Topics include risk factor control, diabetes, hypertension, lipids, medications, aerobic exercise, strength training and flexibility, weight control, reading food nutrition labels, eating out, holiday eating, intimacy, stress, relaxation, cardiac symptoms, and cardiac interventions. The one session on weight control is educational only and does not teach behavioral self-regulation skills.

Compliance*:* We will utilize multiple behavioral management strategies to create a positive exercise environment and promote adherence and retention. These include promptly contacting participants who miss a session, scheduling makeup sessions, and offering individual counseling sessions to discuss strategies to promote attendance and limit obstacles to participation.

Behavioral Weight Loss Intervention

Participants randomized to Rehab+WL will complete the exercise-based cardiac rehabilitation program described above, as well as a behavioral weight loss intervention that incorporates evidence-based dietary practices for achieving weight loss.[15] Specifically, the weight loss intervention will consist of 6 months of a high-intensity, on-site comprehensive lifestyle intervention which includes prescription of a moderately reduced-calorie diet and the use of behavioral strategies to facilitate adherence to diet and physical activity recommendations.[15] Individual calorie goals will be adjusted to achieve a weight loss of at least 5-10% within the 6-month intervention timeframe. This level of weight loss, which is considered "successful weight reduction that leads to decreased risk for development of or amelioration of obesity-related medical conditions and cardiovascular risk factors,[15]" will be achieved through a combination of meal replacements, approved meal plans, and individual nutrition and behavioral counseling with the study registered dietitian (RD) who has experience working with middle-aged and older adults on diet behavior modification. This approach will help to maximize weight loss, as obesity treatment guidelines note that the use of meal replacements is associated with increased weight loss at up to 6 months, in comparison with a balanced deficit diet using only conventional food.[15]

Calorie-Restricted Diet*:* Diet plans will provide a caloric deficit of 500 kcals per day. Energy needs will be calculated based on formulas established by the Institute of Medicine. The lowest calorie level permitted will be 1,100 kcals for women and 1,200 kcals for men. The calorie distribution goal will be 25-35% from protein, <30% from fat, and 45-50% from carbohydrates, consistent with the Dietary Reference Intakes for Energy and Macronutrients.[39] Participants will be asked to consume 2 meal replacements per day (Premier Protein shakes and bars); provided by the study), along with one meal composed of traditional foods (low in fat, high in vegetables), and 1-3 snacks as needed (e.g., cereal bar, fruit, or vegetable). For the meal, patients will follow a weekly menu plan and recipes provided by the study. The food plan will be tailored to individual preferences and energy needs. Participants will be guided by the RD on their food purchasing and preparation of the meals and will be encouraged to consume only what is approved from the menu.

Behavioral Modification*:* During months 1-3, participants will attend weekly individual behavioral counseling sessions with the study RD; individual sessions will be held twice per month during months 4-6. The behavioral sessions will focus on self-monitoring, portion control, mindful eating, coping with

negative thoughts, eating at regular times, and stress management. During these sessions, the RD will review individual progress, solve problems, answer questions, and set weight loss goals. Participants will be encouraged to use relapse-prevention techniques, e.g., managing the environment and adjusting appropriate goal-based daily energy needs.

Compliance: Participants will be asked to record their food and beverage intake in daily logs which will be reviewed weekly by the RD to verify compliance to the diet. The food diaries will also be used as a self-monitoring tool. In addition, body weight will be measured weekly to ensure that participants are losing weight at an appropriate rate. The weekly weigh-in will also serve as a way to increase participant awareness and motivation. If it is evident that participants are not compliant with the diet, additional counseling sessions with the RD will be held to improve compliance. If a participant is not meeting weight loss goals, energy intake will be modified accordingly to produce the desired rate of weight loss. For participants who have difficulty achieving the weight loss goal, we will use a behavioral "toolbox" that includes incentives, home-assessments, or other items as appropriate. We have used these techniques successfully in previous weight loss studies.[40, 41]

Organization of Study Visits

All assessments will be conducted during up to 6 visits including a screening visit, baseline visit, 3-month follow-up visit, and 6-month follow-up visit (**Table 1**). The nature, purpose, and risks of all tests will be explained to participants prior to obtaining their written consent and prior to each test. All assessments will take place by study staff blinded to the participant's treatment assignment. To ensure that staff remain blinded, participants will be asked not to discuss their intervention with the assessor. Additionally, the staff member will remind the participants not to tell them which intervention group they have been assigned to.

As described above, the screening visit will take place on the same day as the standard cardiac rehabilitation consultation or on a separate day, if necessary. After obtaining informed consent, information collected on the patient's medical history, height, weight, and dietary habits will be reviewed by the study coordinator, and patients will be asked to complete the MoCA to confirm eligibility. Patients will also be allowed to sample the shakes and bars that will be used in the study.

The baseline visit will take place at WFBMC in the morning after an 8-hour overnight fast within approximately 1 week following the screening visit. Participants will have their weight and blood pressure measured and will undergo tests to assess arterial stiffness, including carotid-femoral pulse wave velocity (PWV), aortic augmentation index (AIx) and arterial wave reflection magnitude. Blood will be drawn for glucose, insulin, hemoglobin A1c, lipids, complete metabolic panel, complete blood count, cardiac biomarkers, and storage. Following all fasting measures, participants will be given a snack. Medical history and current medications and dietary supplements will be reviewed. Participants will complete the 6MW test and tests of physical function, including the expanded short physical performance battery (SPPB), grip strength, and the Mobility Assessment Tool-short form (MAT-sf). A whole-body DXA scan will be done to assess body composition. Cardiac MRI scans will be conducted in participants who consented prior to July 1, 2019. Participants will have anthropometric measurements taken at their waist, hip, and thigh. The Short Form 36 (SF-36), Pittsburgh Fatigability Scale, Weight Efficacy Lifestyle (WEL), S-Weight, and P-Weight questionnaires will be administered. Sedentary behavior and physical activity will be assessed using the ActivPAL® thigh monitor. Participants will be asked to wear the device continuously for seven consecutive days. Participants will be asked to answer questions as accurately as possible about their activity and monitor use in a daily log for all of the seven days. After completion of all baseline measures, participants will be told which intervention group they have been assigned to.

The first follow-up visit (FV1) will take place at WFBMC in the morning after an 8-hour overnight fast following month 3 of the 6-month intervention. Participants will have their weight, body composition, waist, hip, and thigh circumference, vitals, arterial stiffness, 6MW distance, and physical function

measured. Blood will be drawn for glucose, insulin, hemoglobin A1c, lipids, complete metabolic panel, complete blood count, cardiac biomarkers, and storage. Participants will be provided with a snack. Any changes to medical history and current medications or dietary supplements will be reviewed. The PHQ-9, SF-36, Pittsburgh Fatigability Scale, WEL, S-Weight, and P-Weight questionnaires will be administered. Participants will be asked to wear the ActivPAL thigh monitor continuously for seven consecutive days and record their activity in a daily log. Participants who consented after July 1, 2019 may also complete a series of neurovascular tests, which can be scheduled in conjunction with the FV1 study visit, prior to a cardiac rehab session, or on a separate day.

Table 1: Timeline of Study Assessments

Phase	Screening	Intervention Period		
Month	-1	0	3	6
Visit	SV	BV	FV1	FV2
Outcomes				
6MWD		X	X	X
Physical function (expanded SPPB, grip strength, MAT-sf)		X	X	X
Body weight	X	X	X	X
Height	X			
Waist / hip / thigh circumference		X	X	X
Body composition (DXA)		X	X	X
Quality of life (SF-36)		X	X	X
Fasting lipids		X	X	X
Fasting glucose/insulin		X	X	X
Blood pressure		X	X	X
Cardiac structure and function (MRI)*		X		X
Cardiac biomarkers (CRP, BNP, Troponin I, Troponin T)		X	X	X
Arterial stiffness (PWV, aortic AIx, RM)		X	X	X
Cardiac-specific miRNAs (miR-1, 133a/b, 208a/b, 499)		X	X	X
Baroreflex sensitivity#			X	X
Cerebral autoregulation#			X	X
Cerebral vasomotor reactivity#			X	X
Additional measures				
Cognitive function (MoCA)	X			
Depression (PHQ-9)	X		X	X
Sedentary behavior/physical activity (ActivPAL)		X	X	X
Fatigue (Pittsburgh Fatigability Scale)		X	X	X
Self-efficacy (WEL)		X	X	X
S-Weight / P-weight		X	X	X

6MWD = Six minute walk distance; SPPB = short physical performance battery; MAT-sf = Mobility Assessment Tool - short form; DXA = dual energy x-ray absorptiometry; MRI = magnetic resonance imaging; CRP = C-reactive protein; CK = creatinine kinase; NT-proBNP = N-terminal pro-brain natriuretic peptide; PHQ-9 = 9-item Patient Health Questionnaire; PWV = pulse wave velocity; AIx = augmentation index; RM = reflection magnitude; MoCA = Montreal Cognitive Assessment; WEL = weight efficacy lifestyle

*Cardiac MRI scans will only be conducted in participants who were consented before July 1, 2019

#Neurovascular testing will only be conducted at FV1 and/or FV2 in participants who were consented after July 1, 2019

The second follow-up visit (FV2) will take place at WFBMC in the morning after an 8 hour overnight fast at the end of the 6-month intervention. Participants will have their weight, body composition, waist, hip, and thigh circumference, vitals, arterial stiffness, 6MW distance, and physical function measured. Blood will be drawn for glucose, insulin, hemoglobin A1c, lipids, complete metabolic panel, complete blood count, cardiac biomarkers, and storage. Participants will be provided with a snack. Medical history and current medications and dietary supplements will be reviewed. Cardiac MRI scans will be conducted in participants who consented prior to July 1, 2019. The PHQ-9, SF-36, Pittsburgh Fatigability Scale, WEL, S-Weight, and P-Weight questionnaires will be administered. Participants will be asked to wear the ActivPAL thigh monitor continuously for seven consecutive days and record their activity in a daily log. Participants who consented after July 1, 2019 may also complete a series of neurovascular tests, which can be scheduled in conjunction with the FV2 study visit, prior to a cardiac rehab session, or on a separate day.

After completion of all study visits, participants will be mailed a results packet that includes relevant health information collected over the course of the study.

Outcome Measures

All primary, secondary, and exploratory outcomes will be assessed at baseline and at 3 and/or 6 months by study personnel who are blinded to group assignment. Including the 3-month visit will allow us to evaluate changes in body weight and outcomes within the duration of standard cardiac rehabilitation. We have extensive experience measuring all of these outcomes in our research studies.

Primary Outcome

Feasibility will be assessed in terms of the ability to 1) recruit study participants (i.e., total number randomized divided by total number eligible); 2) retain participants in the study for the full 6 months (i.e., the proportion of randomized participants who return for follow-up testing); and 3) obtain adequate compliance to the prescribed intervention (i.e., total number of exercise/counseling sessions attended divided by total number of sessions prescribed). We anticipate that at least half of the eligible participants will agree to participate and of those who do, <20% will drop out prior to the study end. We also expect to achieve a compliance rate of ≥80%.

Secondary Outcomes

Body weight will be measured using a digital scale. Additional measures of body size/habitus will also be obtained, including height (using a standard wall-mounted stadiometer).

The ***6MW test*** is a valid and reproducible measure of submaximal exercise capacity that reflects the level at which most activities of daily living are performed, predicts clinical events in cardiac patients, and is therefore a clinically meaningful outcome in cardiac rehabilitation studies.[42-44] Participants will be asked to walk at their own maximal pace on an established course, covering as much ground as they can during the allotted time, without running.[45,46] Performance will be measured by the total distance covered in feet. Blood pressure, oxygen saturation, and HR will be measured before, during, and/or after the test.

Physical function will be assessed using 2 performance-based measures and 1 self-report measure. The expanded Short Physical Performance Battery (SPPB) is a modified version of a widely used assessment of lower extremity physical function that consists of 3 standing balance tasks held for 10 seconds each (side-by-side, tandem and semi-tandem), two 4-m walk tests to assess usual gait speed, and 5 repeated chair stands. To minimize ceiling effects and maximize overall dispersion of test scores, the expanded SPPB increases the holding time of the semi- and full-tandem stands to 30 seconds and adds a single leg stand and a narrow walk test of balance (walking at usual pace within lines of tape spaced 20 cm apart). Expanded SPPB scores are continuous and range from 0 to 4, with higher scores indicative of better performance.[47] Grip strength will be measured twice in each hand using an isometric hydraulic hand

dynamometer (Jamar, Bolingbrook, IL). Participants will be excluded from performing the test if they report hand pain or recent hand or wrist surgery. Mobility will be assessed using the MAT-sf, a 10-item computer-based, self-administered assessment that uses animated video clips of 10 different tasks to illustrate various mobility-related challenges that cover a broad range of functioning.[48] Participants provide an assessment of their ability to perform each task on the computer by clicking the appropriate response (yes/no, number of minutes, number of times). Scores range from 30 to 80, with higher scores indicative of better mobility.

Health-related quality of life will be assessed using the Medical Outcomes Study Short Form 36 (SF-36), a self-report measure with well-documented psychometric properties across a wide range of populations.[49] The SF-36 generates eight subscale scores (general health perceptions; physical functioning; role limitations due to physical problems; bodily pain; mental health; role limitations due to emotional problems; vitality; and social functioning) which will be used to derive a physical component summary (PCS) score and a mental component summary (MCS) score, with higher scores indicating more favorable quality of life.

Arterial stiffness will be assessed as carotid-femoral pulse wave velocity (PWV), which is considered the gold-standard measure of arterial stiffness due to its ease of use, high reproducibility, sensitivity to change, and prognostic and clinical utility.[52-58] Carotid-femoral PWV will be measured in the supine position using the SphygmoCor XCEL system (Atcor Medical, Sydney, Australia), which utilizes a piezoelectric Millar tonometer and a thigh cuff to simultaneously record pressure waves in the carotid and femoral arteries, respectively. PWV is calculated by dividing the distance between the carotid and femoral arteries by the pulse transit time.[59]

Blood pressure will be measured with the participant in a seated or supine position after resting quietly for 5-10 minutes. Brachial and central (aortic) blood pressure will be measured using an automated sphygmomanometer and the SphygmoCor XCEL system, respectively.[84]

Hemoglobin A1c will be measured in whole blood using a turbidimetric inhibition immunoassay.

Insulin will be determined by a chemiluminescent immunoassay. Insulin resistance will be estimated using the homeostasis model assessment (HOMA) index.[63]

Tertiary Outcomes

Waist, hip, and thigh circumference will be measured at the mid-point between the highest point of the iliac crest and lowest point of the costal margin in the mid-axillary line, at the level of the maximal gluteal protuberance, and midway between the inguinal crease and the proximal border of the patella, respectively.

Body composition will be measured by dual-energy x-ray absorptiometry (DXA, Hologic Delphi QDR, Bedford, MA) to assess total body fat and lean mass. Whole body scans will be acquired with the participant supine and all scans will be analyzed by our trained technician who is certified by the International Society for Clinical Densitometry and has experience in body composition measurements in middle-aged and older adults.

Depression will be assessed using the 9-item Patient Health Questionnaire (PHQ-9), a brief screening instrument that has been shown to have reasonable sensitivity and specificity for patients with CHD.[30] The PHQ-9 yields both a provisional depression diagnosis and a severity score that can be used for treatment selection and monitoring. PHQ-9 scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression, respectively.

Cardiac structure and function will be assessed by MRI, as previously described.[50,51] LV mass and volumes will be assessed from a series of multi-slice, multi-phase, gradient-echo sequences positioned perpendicular to the long axis of the left ventricle, spanning apex to base (i.e. short axis stack) and will be calculated by summation using Simpson's rule. LV ejection fraction will be calculated as LV stroke volume divided by LV end-diastolic volume multiplied by 100. Cardiac output will be calculated as LV stroke volume multiplied by heart rate. These measurements are routinely obtained during both clinical and research scans.

Cardiac biomarkers that reflect myocardial injury will be measured using standardized procedures. High-sensitivity C-reactive protein (CRP) will be measured using an immunochemiluminometric assay. Brain natriuretic peptide (BNP) will be measured by radioimmunoassay, troponin I will be measured by ELISA, and troponin T will be measured using an electrochemiluminescence immunoassay.

Cardiac-specific microRNAs (miRNAS, small noncoding RNAs that repress target gene expression[64]) including miR-1, miR133a/b, miR-208a/b, and miR-499, which are abundantly expressed in the myocardium, will be assessed using whole blood collected in PAXgene Blood RNA tubes. These and other non-specific miRNAs have emerged as promising biomarkers in the pathophysiology, diagnosis, and treatment of cardiovascular diseases.[65-69] Global miRNA expression will be measured using the nCounter Human v2 miRNA Expression Assay (NanoString Technologies, Seattle, WA), which enables multiplexed direct digital counting of miRNAs.[70]

Arterial wave reflection will be determined via pulse wave analysis using the SphygmoCor XCEL. Indices include aortic augmentation index which is calculated as the ratio of augmentation pressure to pulse pressure and is expressed as a percentage,[60] and reflection magnitude, which is derived using wave separation analysis and is calculated as the ratio of the amplitudes of the forward and backward waves.[61]

Blood lipids, including triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol will be measured in fasted blood samples using enzymatic methods, as previously described.[62]

Blood glucose will be measured in fasted blood samples with the glucose hexokinase method (Bayer Diagnostics, Tarrytown, NY).

Stages and processes of change for weight management will be assessed using the S-Weight and P-Weight, two self-report questionnaires that were designed based on the transtheoretical model.[27,28] The S-Weight consists of five mutually exclusive items to assess readiness to change in order to lose weight. Respondents are asked to choose the stage that best corresponds to their current weight-loss situation: Pre-contemplation, Contemplation, Preparation, Action, or Maintenance. The P-Weight consists of 34 items measuring readiness to engage in dietary and physical activity behaviors based on four processes of change that are implicated in weight management: Emotional Re-evaluation (13 items), Weight Management Actions (7 items), Environmental Restructuring (5 items), and Weight Consequences Evaluation (9 items). Answers are given on a five-point Likert scale ranging from 1 (strong disagreement) to 5 (strong agreement). Scores for each of the four processes of change can be calculated by summing up the subscale scores. Higher scores reflect greater use of a given process. The use of S-Weight and P-Weight will enable identification of which processes of change individuals use the most according to the stage of change they are in.

Exploratory Outcomes

Cerebral Autoregulation will be assessed via continuous blood pressure (BP) and cerebral blood flow velocity (CBFv) monitoring acquired from noninvasive finger arterial pressure measurements and bilateral transcranial Doppler (TCD) imaging of the middle cerebral arteries (MCA), respectively. CA will be measured at rest and during up to 2 sit-to-stand maneuvers, as described.[71-74] The single sit-stand

maneuver will consist of 2 min of sitting, followed by 1 min of standing. Data will be averaged over 3 trials. After a brief recovery period, the repeated sit-stand maneuver will be performed at a frequency of 0.05 Hz (10 s sitting, followed by 10 s standing for 15 cycles), which represents the very low-frequency range where CA is most active under normal circumstances.[75, 76] CA will be calculated in the frequency domain using transfer function analysis (TFA) in accordance with Cerebral Autoregulation Research Network (CARNet) recommendations.[74] Additional CA indices measured in the time domain may also be considered, including the following:[77] 1) autoregulatory index (ARI);[78, 79] 2) rate of recovery (RoR); and 3) mean flow index (Mx).[80, 81]

Baroreflex Sensitivity will be assessed via continuous BP and heart rate (HR) monitoring acquired from noninvasive finger arterial pressure measurements and electrocardiography (ECG) at rest and during the orthostatic challenges described above using validated and published techniques.[82-85] BRS will be calculated by the sequence method (Sequence UP, DOWN and TOTAL) and the frequency method (i.e., low-frequency and high-frequency alpha indices), as described.[82-85]

Cerebral Vasomotor Reactivity (CVMR) will be determined by inducing hypocapnia via hyperventilation, followed by a brief period of spontaneous breathing. Next, participants will be asked to inhale a gas mixture containing 5% CO_2 through a non-rebreathing mask until a stable plateau of CBFv is reached. With this protocol a wide range of changes in end-tidal CO_2 can be obtained. CVMR will be expressed as the ratio of CBFv changes over changes in end-tidal CO_2, as well as the percent change in CBFv across the full range from hypocapnia to hypercapnia relative to resting CBFv.[86, 87] Absolute and relative changes in BP, HR, cerebrovascular resistance, and end-tidal CO_2 across the full spectrum will also be examined. This protocol is used regularly in the Diagnostic Neurology clinic at WFBH.

Process Measures

The following measures will be collected at baseline, 3, and 6 months to assess changes in key lifestyle behaviors.

Total exercise volume in kilocalories per week will be calculated based on exercise intensity, duration, and frequency of sessions.

Physical activity and sedentary behavior will be objectively assessed using accelerometry with the ActivPAL® monitor. Participants will be asked to wear the device continuously for 7 consecutive days at each time point. The thigh monitor will be attached directly onto the skin and positioned on the front of the thigh, roughly 1/3 of the way between hip and knee with the stick man standing up. Participants will be asked to complete each question for all of the seven days as accurately as possible. Data will be downloaded at the end of each 7-day period and cleaned and summarized for statistical analyses.

Fatigability (fatigue in the context of a standardized task) will be assessed using the Pittsburgh Fatigability Scale, a 10-item scale that assesses physical and mental fatigability, with scores ranging from 0-50 (higher scores indicate greater fatigability).[88] This is an important measure to consider as individuals often "self-pace" or lower their level of activity or exertion in performing a task to reduce their fatigue.

Self-efficacy will be assessed using the Weight Efficacy Lifestyle Questionnaire (WEL), a validated, 20-item questionnaire that is sensitive to change and highly predictive of weight loss.[89-99] Participants will be asked to rate their confidence in resisting the desire to eat in 5 situational domains (availability, negative emotions, physical discomfort, positive activities, and social pressure) using a 10-point scale that ranges from 0 (not confident) to 9 (very confident).[100] Subscales scores will be summed to yield a total self-efficacy score.

Descriptive Variables and Potential Confounders

Because this is a randomized trial, we have no *a priori* reason to expect confounding factors to be unbalanced between intervention groups. Nevertheless, the following variables will be evaluated to estimate their influence on the outcomes of interest.

Demographics and co-morbidities: Information regarding age, race/ethnicity, tobacco use, alcohol intake, socioeconomic status (i.e., education, insurance status, employment status), and co-morbidities will be ascertained at the screening visit. The Charlson comorbidity index will be used to quantify disease burden.[101]

Medication use: Participants will be asked to bring in all medications and dietary supplements for a "brown bag" review during the screening visit. Medication name and dosage will be recorded and coded using the Iowa Drug Information System (IDIS).[102] Participants will be asked to inform staff of medication changes, which will be reviewed at the 3- and 6-month study visits using a structured medication inventory form.

Time to enrollment: Delay time will be defined as the number of days between hospital discharge and start of cardiac rehabilitation.

Recurrent Events

Cardiovascular events and rehospitalizations will be assessed by staff masked to group assignment. Pertinent medical records will be obtained to confirm all events and procedures. Hospitalizations will be categorized using the Clinical Classifications Software system from the Agency for Healthcare Research and Quality (https:// www.hcup-us.ahrq.gov/ toolssoftware/ccs10/ ccs10.jsp). The study physician (masked to group assignment) will adjudicate each outcome using standardized criteria.

Analytical Plan

Sample Size

Assuming that at least 50% of eligible patients will be interested in participating in the study and meet the full inclusion/exclusion criteria, we anticipate enrolling 1-2 participants per week. Based on a conservative dropout rate of 20%, we expect a final sample size of 16 per group. While this pilot study is not designed to provide sufficient statistical power to detect differences in the measured outcomes, we will obtain estimates of treatment efficacy and estimate the variability of outcome measures in this population to use in the design of a larger, more definitive trial.

Data Cleaning

We will examine the distributions of the outcome variables and the need for any transformations to approximate conditional normality for further analysis. Summary statistics will be calculated, including means, standard deviations, quartiles, and ranges for continuous variables, and counts and percentages for categorical variables. Range and validation checks will be performed on all variables in collaboration with study personnel. We will examine the distributions of all the variables, identify the potential outliers and influential points, and clean any unreasonable data.

Statistical Analyses

All randomized participants will be included in their original intervention group regardless of compliance with the study protocol (i.e., an "intent to treat" analysis). Chi-square tests will be used to assess group differences in retention and compliance rates. Longitudinal data for the outcome variables will initially be presented graphically (e.g., spaghetti plot) with individual trajectories over time. The graphical displays will help to highlight aggregate patterns of potential scientific interest and identify unusual values. The mixed-model repeated measures ANCOVA model will be used to determine whether Rehab+WL leads to greater improvements in CHD and neurovascular outcomes than Rehab alone. A

subject random effect will be included to account for the fact that multiple measurements within a participant over time are not independent. Fixed effects will include sex and obesity severity (i.e., the randomization stratification factors), clinical site (WFBMC, DMC, or LMC), the baseline (pre-randomization) value, time (3 or 6 months), the group assignment, and the group by time interaction. Hypothesis tests for intervention effects at the 3- and 6-month study visits will be performed using contrasts of the 3- and 6-month intervention group means. The primary comparison will be based on an intervention contrast at 6 months. Overall comparisons between groups across follow-up visits will be obtained using a contrast to compare average effects across both follow-up visits. Associations with the stage of change (S-Weight) and P-Weight scores will be examined to determine their influence on recruitment, retention, adherence, CHD outcomes, and neurovascular outcomes. If a particular intervention group has a markedly higher dropout rate, we will attempt to identify baseline covariates that predict attrition in secondary analyses. If such covariates can be identified, the analysis of the outcome measure will adjust for those covariates. Other factors that may influence the measured responses to the interventions such as the number of comorbidities, socioeconomic status, time to enrollment, medication use, and magnitude of weight loss will also be evaluated. Differences in intervention process measures (e.g., total volume of exercise) and compliance measures (e.g., attendance at diet and exercise sessions) will also be examined to assess the extent to which these variables contribute to the outcomes.

Human Subjects Protection

Subject Recruitment Methods

Inpatient recruiting will be performed primarily via a joint effort by the study coordinator and the program manager, with supervision by the study physician (Dr. Kitzman, Co-I) and the study PI (Dr. Brinkley). In addition, the Sticht Center on Aging supports a Recruitment Core service to assist investigators with targeted recruitment strategies. This service, which has successfully recruited participants for 8 weight loss trials since 1997, will also be available for the proposed study. WFBH has a systematic referral process in place to help increase access to and enrollment of eligible patients in cardiac rehabilitation. The study coordinator, with help from specially-trained nurses serving as cardiac wellness coordinators and cardiac rehabilitation staff, will assess ability and willingness to participate. Currently, 50-80 patients are referred to cardiac rehabilitation each month and 6-8 new patients start the program each week. Tapping into this automatic referral system will allow us to easily identify potential candidates for our study and interact with them early in the referral process to assess eligibility. Informational study flyers will also be included in discharge packets and letters will be mailed to patients admitted to WFBH with a CHD-related diagnosis or procedure. Significant pre-screening will be performed by review of clinic, hospital, echocardiography, and cardiac catheterization records, as well as digitally copied ECGs and other relevant diagnostic and procedure reports. Further screening using data forms specifically designed for this purpose will be conducted by telephone and in-person (on the same day as the consultation or at a separate visit, if necessary). Every effort will be made to enroll participants within 2 weeks of hospital discharge (i.e., 3 weeks after index event).

Informed Consent

Prior to any data collection, all participants must provide written informed consent to participate in the study and complete a HIPAA authorization form in accordance with the Wake Forest School of Medicine Institutional Review Board (IRB) policies. Written informed consent will be obtained by research staff after explanation of the entire protocol. Staff will explain the purpose, methods and extent of the study to prospective participants who will then be asked to read the informed consent form and ask questions. The form will be written in simple, easy to understand language. All of the key aspects of the study will be verbally reviewed. Staff will be provided with a structured checklist for this purpose. Participants will be asked specifically about the storage of blood samples for use in future studies. In order to participate in this study, they must be willing to provide blood samples for future research. At any time, participants will be able to request that their samples or data be withdrawn from current or future use by contacting

the PI. Participants will also be asked to complete a medical records release form so that study staff can adjudicate any hospitalizations and deaths that occur over the course of the study. One copy of the consent form will be placed in the participant's medical record which will be kept in a locked file and another copy will be given to the participant for his/her records.

Potential Risks

There are potential risks associated with some aspects of the proposed research study. However, the intervention procedures have been designed to minimize the danger of major complications, and all tests are performed by trained, experienced research staff who will be supervised by qualified medical personnel as needed. Risks associated with specific procedures and the interventions are discussed below.

1) Questionnaires: The interviews and questionnaires participants complete in this study are of minimal risk. These include the Montreal Cognitive Assessment (MoCA), 9-item Patient Health Questionnaire (PHQ-9), Medical Outcomes Study Short Form 36 (SF-36), Pittsburgh Fatigability Scale questionnaire, Weight Efficacy and Lifestyle (WEL) questionnaire, and the stages and processes of change questionnaires for weight management (S-Weight and P-Weight, respectively). Care will be taken to ensure participant privacy and confidentiality while discussing personal and health information. It is possible that some patients with previously undiagnosed mild cognitive impairment (MCI) or major depressive symptoms will be found to have these problems. Patients with MCI and major depression at screening will be excluded from further participation and referred for appropriate medical follow-up. Study participants who develop signs of mild-to-moderate depression at the follow-up visits will be referred to outpatient counseling services through CareNet. Those with moderate-to-severe depression will be referred to their primary care physician, or psychiatry if necessary, for further evaluation.

2) 6-Minute Walk Test: There is a slight risk of falling during this test, and occasionally participants become short of breath or fatigued and must rest and/or stop the test. To minimize risk, American Thoracic Society (ATS) guidelines will be followed for performing and stopping the test. Participants will be closely monitored during the test, including measurement of heart rate and oxygen saturation. We will also make sure that the walking path is clear and that trained staff is always nearby. We have had no serious adverse events during or after 6MW tests in over 500 middle-aged and older study participants.

3) Physical function tests: There is a small risk of injury during the physical function tests, such as muscle strains or pulls, falls, or joint injury. Risks will be minimized by having experienced/ trained staff conducting these assessments. A warm-up and range of motion practice will be conducted before testing. If a participant reports pain, dizziness, or other medical problem, the test will be terminated.

4) DXA scans: Other than some exposure to radiation, there are no risks associated with the DXA scans. Participants will receive approximately 3 mrem of radiation from the whole body DXA scans (includes 1 baseline and 2 follow-up scans) over the course of 6 months. This amount is equal to 0.01 times the amount of natural background radiation that the average person in the United States receives each year (300 mrem). The potential long-term risk from this radiation is uncertain, but these doses have never been associated with any definite adverse effects. To manage this modest amount of risk, all scans will be performed and analyzed by a trained DXA technician who is certified by the International Society for Clinical Densitometry and has vast experience in body composition measurements in middle-aged and older adults.

5) Cardiac MRI Scans: There are no risks associated with the MRI scans. Some people may experience discomfort in the scanner if they are uncomfortable in tight places or if the noise from

the scanner bothers them. To minimize this discomfort, participants will be screened for claustrophobia and will be asked to wear earplugs.

6) Blood Draw: Participants may experience slight discomfort, bruising and/or bleeding where the needle is inserted. Occasionally, some people become dizzy, lightheaded, or feel faint. Infection may also occur on rare occasions. To minimize these risks, blood will be drawn only by trained and experienced phlebotomists.

7) Cardiac Rehabilitation: The risks associated with the prescribed aerobic and resistance exercises are minimal and include loss of balance and a risk of injury from falls while walking, fatigue, and muscle strains or sprains. Other potential risks from exercise, such as an abnormal heart rhythm, a heart attack, a stroke, or even death, are rare (less than 1 in 50,000 patient hours of exercise). To minimize the risk of injury and ensure the safety of study participants, standard procedures for exercise progression will be followed in accordance with the American College of Sports Medicine (ACSM) recommendations. The intensity of exercise will gradually increase over the first few weeks, and each session will include warm-up and cool-down activities, as well as light stretching. All exercise sessions will be supervised by exercise physiologists who are trained in advanced cardiac life support and each participant's response to exercise (heart rate, blood pressure, perceived exertion) will be closely monitored before, during, and after each session. Additionally, a fully stocked crash cart will be available with all necessary emergency equipment (drugs, defibrillator, airway management) to deal with medical emergencies. Institutional and community EMS services will also be activated if needed.

8) Weight Loss: The risks of caloric restriction are small and include excessive weight loss. These risks will be minimized by the direct involvement of a registered dietitian and medical oversight by the study physician. To ensure safety of study participants, food plans will be tailored to individual preferences, the lowest calorie level permitted will be 1,100 kcals for women and 1,200 kcals for men, and calorie goals will be closely monitored to minimize rapid or excessive weight loss. Weight loss interventions also have the potential to increase risk of hypoglycemia and hypotension. To minimize these risks, study staff will contact the primary care provider of any participant treated with glucose- or blood pressure-lowering medications who develops symptomatic hypoglycemia or hypotension to discuss adjustment or discontinuation of these medications. If a primary care provider cannot be contacted in a timely manner, the study physician may elect to adjust these medications and the personal care provider will be notified by phone and in writing. We have previously completed 8 weight loss trials in a variety of populations with no reports of significant adverse effects.

9) Neurovascular Testing: Risks and side effects related to TCD monitoring include reaction from the gel and risk of skin irritation from the TCD headband. However, these are very rare occurrences and no adverse events associated with TCD usage have been reported in the literature. The ECG electrodes may also cause some skin irritation or a mild rash; however, this usually goes away without treatment once the electrodes are removed. Some people may experience discomfort from the finger cuff squeezing their fingers. If this occurs another finger can be used for the assessment. Some fatigue during the sit-stand tests is normal and some people may feel claustrophobic when the non-rebreathing mask is placed over their nose and mouth; if this discomfort persists or if the participant experiences pain, dizziness, or other medical problem, the test will be terminated. Study staff will assess for any signs of pain or intolerance throughout the testing procedure.

Medical Clearance

The study physician and/or PI will personally review the relevant medical records to ensure inclusion/exclusion criteria are met and that it is safe for the participant to participate. Study results related to blood pressure, hemoglobin A1c, glucose, lipid, and other relevant lab values that are obtained during scheduled study visits will be provided to each participant's primary care provider in a form that clearly indicates abnormal values and ranges. When a cardiovascular event is discovered during the trial, the study physician will decide whether it is permissible for the participant to continue the intervention. If the intervention is discontinued for safety reasons, it may be resumed after consultation with the participant's primary care provider.

Medical Costs

This study will involve a partnership with the Cardiac Rehabilitation Program at WFBH. Costs to attend cardiac rehabilitation for 6 months will be provided for all study participants.

Study Incentives

Participants will be provided with $50 for each study visit completed ($150 total for completing all study visits). This incentive is designed to help offset the cost of traveling to/from the medical center for study-related visits and purchasing food or prepared meals in accordance with the individualized meal plans.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify participants, and maintaining all study information in a secure manner. To help ensure participant privacy and confidentiality, only a unique study identifier will appear on data collection forms. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed at least six years after the study ends consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff. We will also use the WFU Pepper Center's appointed Data Safety Monitoring Board. This board meets twice a year and reviews all studies that are supported by the WFU Pepper Center. A copy of the report will be submitted to the IRB after each meeting.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

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