



Published in final edited form as:

Am Heart J. 2015 November ; 170(5): 986–994.e5. doi:10.1016/j.ahj.2015.08.006.

Lifestyle Modification for Resistant Hypertension: The TRIUMPH Randomized Clinical Trial

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Abstract

Background—Resistant hypertension (RH) is a growing health burden in this country affecting as many as one in five adults being treated for hypertension. RH is associated with increased risk of adverse cardiovascular disease (CVD) events and all-cause mortality. Strategies to reduce blood pressure in this high risk population are a national priority.

Methods—TRIUMPH is a single site, prospective, randomized clinical trial (RCT) to evaluate the efficacy of a center-based lifestyle intervention consisting of exercise training, reduced sodium and calorie DASH eating plan, and weight management compared to standardized education and physician advice in treating patients with RH. Patients (N=150) will be randomized in a 2:1 ratio to receive either a 4-month supervised lifestyle intervention delivered in the setting of a cardiac rehabilitation center or to a standardized behavioral counseling session to simulate real-world medical practice. The primary end point is clinic blood pressure; secondary endpoints include ambulatory blood pressure and an array of CVD biomarkers including left ventricular hypertrophy, arterial stiffness, baroreceptor reflex sensitivity, insulin resistance, lipids, sympathetic nervous system activity, and inflammatory markers. Lifestyle habits, blood pressure and CVD risk factors also will be measured at one year follow-up.

Conclusions—The TRIUMPH randomized clinical trial (ClinicalTrials.gov NCT02342808) is designed to test the efficacy of an intensive, center-based lifestyle intervention compared to a

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Disclosures: None

Clinical Trial Registry: NCT02342808

standardized education and physician advice counseling session on blood pressure and CVD biomarkers in patients with RH after 4 months of treatment, and will determine whether lifestyle changes can be maintained for a year.

Keywords

Resistant hypertension; DASH diet; exercise; obesity; cardiac rehabilitation

BACKGROUND

The term “resistant hypertension” (RH) is defined as blood pressure (BP) that remains above goal (e.g., systolic blood pressure [SBP]>140 mm Hg and/or diastolic blood pressure [DBP]>90 mm Hg), despite adherence to a regimen of 3 or more optimally-dosed antihypertensive medications of different classes, one of which is a diuretic, or the need for 4 or more antihypertensive agents to achieve goal.¹ With the growing prevalence of hypertension in this country, RH is a major public health concern, affecting more than 7.5 million Americans.¹⁻³ Patients with RH are 50% more likely to experience a cardiovascular (CVD) event, including stroke, kidney failure, myocardial infarction, and death, compared to patients with controlled BP.⁴⁻¹⁰ There is an urgent need for developing RH management strategies to lower BP as well as to reduce the high risk of CVD-related events.¹¹

Lifestyle modifications, including exercise training and dietary modification, are of proven efficacy in lowering BP in unmedicated patients with hypertension and are often recommended as the first step for treating high BP.¹² The Dietary Approaches to Stop Hypertension (DASH) diet has been shown to lower BP in hypertensive patients who are not treated with drugs.¹³⁻¹⁸ Moreover, when the DASH diet is combined with exercise and caloric restriction, even greater, and quite marked, BP reductions can be achieved.^{19,20} However, the efficacy of these lifestyle modifications in RH patients who are refractory to medical therapy is unknown.

In a recent editorial, Hayward and Krumholz²¹ provide a compelling argument that treatment decisions should be made on the basis of patients’ overall CVD risk status, with the objective of lowering this risk as much as possible. Effective lifestyle interventions afford the opportunity for not only reduction of BP, but also for modification of multiple risk factors, which can result in significant reduction of overall CVD risk in RH patients. Patient-centered outcomes, including quality of life, may also improve with lifestyle modifications. A premise of the TRIUMPH trial is that unhealthy lifestyles, including poor food choices and sedentary living, play an important role in the development and persistence of RH and that modifying these unhealthy behaviors will arrest and potentially reverse the disease process. A further premise is that despite the apparent motivation of patients to adopt a healthy lifestyle, a structured intervention program is needed for them to achieve and maintain a therapeutic response. Unhealthy behavior patterns are typically well-entrenched and have long-term rather than short-term negative consequences, and lifestyle changes require a significant daily commitment to effortful planning and recalibration of life priorities. Figure 1 depicts a model by which poor nutrition and lack of exercise may adversely impact BP in this population, and how the complex interplay of autonomic,

metabolic, inflammatory, cardiac, and vascular function may be both a cause and consequence of RH.

Novel Invasive Approaches to the Treatment of Resistant Hypertension

The failure of treatment with antihypertensive drugs to adequately lower BP in RH patients has prompted the development of novel non-pharmacological interventions. One approach is carotid baroreceptor activation to attenuate sympathetic activity and augment cardiac vagal control.^{22,23} Although this technique has been successful at achieving modest reductions in BP in early clinical trials, it requires permanent implantation of a device and approximately 25% of patients may experience procedure-related adverse outcomes.^{24,25} Recently, a small, open-label randomized trial of a central iliac arteriovenous anastomosis produced with a coupler device demonstrated significant reductions in both SBP and DBP, but much remains to be learned about the longer term efficacy and safety of this intervention.²⁶ Another initially promising procedural approach to the treatment of RH is catheter-based renal sympathetic denervation.²⁷ The SYMPLICITY HTN-2 trial²⁸ generated much excitement in the medical community by suggesting that percutaneous renal sympathetic denervation could lower clinic SBP by as much as 30 mm Hg in RH patients.²⁹ However, SYMPLICITY HTN-3,³⁰ a more rigorously designed and pivotal multi-center trial of catheter-based renal denervation performed in the United States, failed to meet its primary efficacy endpoint of a reduction in clinic-based SBP \geq 5 mm Hg. This disappointing outcome has tempered the prospects for widespread utilization of renal denervation in the management of RH in the near future, and underscores the need for new avenues of investigation for non-pharmacological approaches to lowering BP and reducing CVD risk in RH patients.

Back to the Future: Potential Benefits of Lifestyle Modification in Patients with Resistant Hypertension

Although the value of lifestyle interventions in patients already taking antihypertensive medications has not been widely studied, the available evidence, acquired primarily in patients treated with 1 or 2 drugs, appears promising. Regular exercise alone lowered DBP and led to regression of left ventricular hypertrophy (LVH) in a small study of medicated African-American men with uncontrolled hypertension,³¹ and the TONE study demonstrated that in elderly patients receiving antihypertensive monotherapy, sodium restriction and weight loss resulted in improved BP control.³² Surprisingly, there are limited data describing the effects of the DASH diet in medicated hypertensive patients. In a study of 55 hypertensive patients treated with an angiotensin receptor blocker (ARB), the DASH diet was associated with a 5 mm Hg greater reduction in ambulatory SBP compared to patients taking the ARB with their usual diet.³³ The ADAPT trial³⁴ was an Australian study of hypertensive patients treated with 1 or 2 drugs in which an intervention designed to promote consumption of a modified DASH diet resulted in a modest (4/2 mm Hg), but statistically significant, reduction in ambulatory BP and reduced dependence on antihypertensive medications. In the DEW-IT study,³⁵ a 9-week 'feeding' study of 44 overweight adults on a single BP-lowering agent, the DASH diet coupled with weight loss also resulted in significant BP reductions.

Surprisingly, lifestyle modification has not been rigorously evaluated in patients with RH. Several small studies, however, suggest that changes in diet and physical activity have the potential to lower BP substantially in these individuals. For example, in a study of 12 subjects with RH, 24-hour ambulatory BP was 23/9 mm Hg lower on a 50 mmol/d (1150 mg/d) sodium diet compared to a 250 mmol/d (5750 mg/d) sodium diet.³⁶ In this study, however, the treatment periods were short (7 days) and all food was prepared in a clinical research center; whether similar results could be achieved in the longer-term and in the absence of specially prepared meals is unclear. In another small study, Dimeo et al.³⁷ examined the value of physical activity in 50 patients with RH who were randomized to thrice weekly treadmill exercise or a control condition; exercise decreased ambulatory daytime BP by 6/3 mm Hg. Thus, preliminary evidence suggests that lifestyle modifications may be effective in reducing BP in RH patients, but such efforts need to be examined in more rigorous RCTs.

METHODS

TRIUMPH is a randomized controlled trial (RCT) designed to evaluate whether an intensive, medically-supervised lifestyle intervention can achieve clinically significant BP lowering in medicated patients with RH. In addition to evaluating the primary endpoint of clinic BP, the study will also examine effects on 24-hour ambulatory blood pressure (ABP), along with a constellation of CVD risk factors that are common in RH patients and that contribute to the increased risk associated with uncontrolled BP.

One hundred fifty patients with RH will be evaluated and randomized with 2:1 allocation to one of two treatment groups: (1) Center-based Lifestyle Intervention (C-LIFE) or (2) Standardized Education and Physician Advice (SEPA). Participants will be evaluated at (a) baseline; (b) after a 4-month intervention; and (c) 1 year after randomization. The study design is depicted in Figure 2.

Participants

RH is defined as SBP that is higher than 140 mm Hg, despite treatment with 3 optimally-dosed antihypertensive medications of different classes, including a diuretic,¹² or the need for 4 or more drugs to achieve a SBP \leq 140 mmHg.

Inclusion Criteria—Recruitment will target individuals with documented RH within the last 6 months. Individuals treated for two or more weeks with at least 3 antihypertensive medications of different classes (at a stable dosage), including a diuretic, with clinic SBP \geq 140 mm Hg or DBP \geq 90 mm Hg, will be eligible. Individuals being treated with 4 or more antihypertensive medications (including a diuretic) with SBP \geq 130 or DBP \geq 85 mm Hg also will be eligible. In addition to hypertension, other inclusion criteria include: overweight or obese (e.g., body mass index [BMI] 25-39.9 kg/m²), sedentary (exercise $<$ 30 min/week), age 35-80 years, and willingness to be randomized to either of the 2 treatment groups.

Exclusion criteria—Secondary hypertension, severe chronic kidney disease defined as an estimated glomerular filtration rate [GFR] $<$ 45 ml/min/1.73m², moderate-severe ischemic heart disease (Canadian Cardiovascular Society Class 3 or 4 angina or evidence of ischemia

at <85% heart rate reserve on treadmill testing), severe heart failure (New York Heart Association Class 3 or 4), high grade arrhythmias, severe valvular heart disease, severe asthma or chronic obstructive lung disease, diabetes requiring insulin, musculoskeletal or neurologic problems that would preclude participation in aerobic exercise training, current major psychiatric disorder or active drug abuse, current alcohol consumption >14 drinks/week, prior gastric bypass surgery, a life-limiting comorbid medical condition such as cancer, or 'pseudoresistant' hypertension due to medication non-adherence or due to the white coat effect.³⁸

Screening Procedures to Determine Eligibility for the TRIUMPH Trial

All eligible patients will undergo clinic blood pressure and medical screening, physical examination, and body weight assessment. Blood pressure will be determined according to JNC 7 guidelines.³⁹ Screening assessments also will include measures of serum creatinine and eGFR, electrolytes, HbA1c, and urinary albumin/creatinine ratio to screen for secondary hypertension and other conditions that would preclude patients from safely participating in the study and to assess comorbidities and target organ manifestations of hypertension. The most common causes of secondary hypertension are CKD and primary hyperaldosteronism. All patients will have baseline measurements of serum creatinine to assess renal function, and renin and aldosterone levels to exclude primary hyperaldosteronism. Thyroid stimulating hormone will be measured to exclude clinically significant thyroid disorders. We will not screen for other secondary causes of hypertension because these conditions tend to be rare (e.g., pheochromocytoma) and/or the impact of current therapies are inconclusive or provides only marginal BP lowering benefit (e.g., renovascular disease and obstructive sleep apnea).

Medication Reconciliation—Treatment regimens will be documented by having participants bring their actual medications to the research clinic and confirmed with referring physicians. To facilitate assessment of medication changes, the intensity of therapy will be quantified as the Daily Defined Dose (DDD) using a method developed by the World Health Organization. The DDD is a system for quantification of drug amount designed to enable comparison across drug classes (e.g., 1×DDD=150 mg irbesartan or 5 mg amlodipine)⁴⁰ and was previously used in the BP Guide and TASMIN-SR studies.^{41,42}

Medication Adherence Screening—Because patients who are non-adherent to their antihypertensive medications could be erroneously classified as RH, we will perform an initial screen for medication adherence using the Morisky Medication Adherence Measure.⁴³ This 8-item scale was developed from the well-validated and widely-used 4-item version⁴⁴ with the objective of specifically evaluating medication adherence in patients with hypertension. The scale has established reliability and validity⁴⁵ and is related to BP control, with a score ≥3 identifying patients with poor BP control due to non-adherence with a sensitivity of 93%.⁴³

Treatment Conditions

Participants will be randomized to one of two treatment arms and encouraged to maintain their prescribed antihypertensive medications at the discretion of their personal physicians, unless contraindicated by safety issues.

(1) Center-based Lifestyle Intervention (C-LIFE): The 4-month C-LIFE intervention will consist of 4 components delivered by our research staff at participating community CR centers:

(i) Diet: Participants will receive instruction on the DASH diet with caloric and sodium restriction (2300 mg/day) and feedback on their adherence to the diet in 16 half-hour weekly sessions. The goal of the weekly sessions is to assist participants in knowing how to buy and prepare the appropriate foods, to enhance their motivation to choose to eat those foods, and to overcome obstacles to following the diet. The nutritionist will utilize motivational interviewing strategies as a way to encourage participants to make the needed changes. A key component, used in the DASH, PREMIER, and ENCORE studies and incorporated into the proposed intervention, is motivational enhancement to reinforce commitment and confidence for behavior change and to help participants explore and resolve ambivalence.^{46,47} Specific efforts to provide culturally-sensitive adaptations of the diet will be provided as our prior work indicated that African-American participants may have difficulty adopting the DASH diet.⁴⁸ Greater emphasis will be placed on the personal, financial, and cultural needs of the participants while they attempt to adopt the DASH diet and reduce dietary sodium (2300 mg/day), and thus provide an individually tailored intervention.

(ii) Behavioral Weight Management: The Weight Management program will consist of 16 half-hour weekly sessions that emphasize the initiation of eating behavior changes, individualized problem-solving, and strategies to facilitate the transition to a long-term self-care plan that is designed to prepare participants to maintain treatment gains on their own following termination of treatment. The weight management employed in TRIUMPH will include focus on the attitudes and skills needed to develop and implement a long-term self-care health plan.

The weight management intervention includes standard cognitive and behavioral strategies with a particular emphasis on the importance of self-monitoring as a strategy to initiate behavior change and an understanding of the roles of motivation for change and automaticity of behavioral patterns in maintaining behavioral changes. Self-monitoring of DASH food goals is used to enhance compliance with the recommended dietary content, and appetite monitoring is used to regulate the amount of food eaten. Appetite Awareness Training (AAT) serves to enhance portion control, facilitate reductions in caloric consumption, and reduce perceptions of deprivation by raising awareness of internal fullness cues. Weekly weight monitoring is to be continued indefinitely as small increases (which are more easily reversed) are not always noticeable. The weight management training will emphasize individualized problem-solving to remove barriers to adherence. The syllabus for the program is provided in an Appendix (Table S1).

(iii) *Supervised Exercise*: Participants initially will exercise at one of the designated CR facilities 3 times per week at a level of 70-85% of their initial heart rate reserve, determined at the time of their baseline treadmill test.⁴⁹ The exercise routine will consist of 10 minutes of warm up exercises, 30-45 minutes of aerobic exercise, and 10 minutes of cool down exercises. Patients with pre-exercise SBP levels >200 mm Hg or DBP >110 mm Hg will not be permitted to exercise; exercise will be stopped immediately if patients' SBP values exceed 250 mm Hg or DBP levels exceed 115 mm Hg. While exercise alone has been shown to be of limited value in reducing BP⁵⁰ and in inducing weight loss,⁵¹ continued exercise and physical activity are widely recognized as being critically important for successful weight maintenance.⁵² Therefore, participants will be counseled to develop a plan to remain active and to exercise on their own, using strategies previously employed to help patients transition from supervised to home-based exercise protocols.^{53,54}

(iv) *Maintenance*: Participants will be prepared to maintain all components that constitute the lifestyle intervention (i.e., DASH eating plan, limited sodium consumption, weight management, and exercise). The C-LIFE intervention will emphasize the transition to self-care by carefully preparing participants to meet the challenges of maintaining lifestyle changes on their own. We hope to maximize the likelihood that those participants who show improvements with treatment will be able to maintain those improvements over time, especially since CR programs do not offer provision for long-term support for behavior change. Because patients with RH currently have few options to lower their BP and hypertension is a chronic disease, it is particularly critical to teach patients to establish a life-long self-care plan.

(2) Medical Management with Standardized Education and Physician Advice (SEPA):

Although patients will be encouraged to achieve an ideal body weight and engage in exercise as part of routine counseling in primary care, no special programs will be provided that enhance patients' ability to comply with these recommendations. The SEPA arm will consist of routine medical care provided by patients' primary care physicians supplemented by an educational session on hypertension management. Patients will receive a dietary consultation and an individualized exercise prescription delivered by a health educator. In order to compare the intensive, structured C-LIFE program with patients' own efforts at adhering to physician advice, patients will be free to engage in their own diet and exercise programs, which we will document over the course of the trial. Referral for an individual consultation with a nutritionist and exercise specialist is an option that is available to physicians in the care for patients with hypertension, and will be standardized at its optimal level of implementation for this research protocol.

Assessments

Blood pressure will be obtained in the clinic and during daily life using 24-hr ambulatory blood pressure monitoring (see Table 1 for assessment methods and testing schedule). In addition to measuring BP, we will assess an array of CVD biomarkers including left ventricular hypertrophy (LVH), cardiovascular hemodynamics (including cardiac output and systemic vascular resistance), arterial stiffness, endothelial function, baroreflex sensitivity,

metabolic factors such as glucose and insulin resistance, inflammatory markers, and aerobic capacity. We also will document the effects of the interventions on relevant lifestyle habits including physical activity, body weight, and diet.

In addition to better BP control, several patient-centered outcomes that could represent important benefits of a lifestyle intervention program will be assessed. These include improvements in other risk factors (e.g., hypercholesterolemia and diabetes) and overall CVD risk⁵⁵ and improved quality of life. A detailed description of the measures obtained in the TRIUMPH study is available in the Appendix (Table S2).

Follow-up

Participants will be followed at 1-year post-randomization (8 months after completion of the 4-month intervention program). All participants will be asked to report any changes in BP medications or other interventions to reduce BP that they may have initiated (under the care of their own physicians). Medication changes will be incorporated into our data analytic plan described below. At 1 year following randomization, measures of clinic BP, ABP, CVD biomarkers, body weight, dietary and exercise habits, and QoL will be reassessed. At the follow-up visit, patients will be asked to bring with them all medications that they are currently taking, so that any adjustments to their antihypertensive therapy can be documented. Patients will also be queried as to whether they participated in any supplemental programs to lose weight (including bariatric surgery), diet, or engage in exercise. This naturalistic follow-up has been used in prior work⁵⁶⁻⁵⁸ and yields important information regarding maintenance of lifestyle habits over time and will be used to help interpret any group differences in BP and CVD biomarkers after 1 year. We also will document a number of clinical endpoints including cardiovascular death, non-fatal MI, non-fatal stroke or transient ischemic attack, coronary revascularization, hospitalization for hypertension, angina, or heart failure, and progression to end-stage renal disease during a follow-up period of up to 5 years.

DATA ANALYSIS

We will evaluate the primary outcome, clinic SBP, at the immediate post-treatment measurement occasion (4 months), with treatment assignment (C-LIFE vs. SEPA) as a between subjects factor, and ethnicity, gender, age, diabetes/chronic kidney disease, baseline medication adherence, and pre-treatment clinic SBP as covariates, selected *a priori*.⁵⁹ We will conduct an ancillary analysis in order to evaluate the possible role of change in BP medication on the treatment effect by adding the DDD measure as a covariate in the models testing treatment effects. Ambulatory daytime SBP will be evaluated as a supportive analysis, using the same modeling approach as above. Analysis of additional outcomes, including ambulatory and clinic DBP, body weight, aerobic capacity, dietary intake, LV mass and relative wall thickness, CVD biomarkers, and patient-centered outcomes will be conducted using the same modeling approach. For secondary outcomes, we again will use separate models for each outcome, using Benjamini and Hochberg's⁶⁰ False Discovery Rate correction for multiple testing. All analyses of primary and secondary outcomes will adhere to the intent-to-treat principle, using multiple imputation for missing data with Harrell's `aregImpute` algorithm in R. Mediation analyses will be carried out following the bootstrap

procedures described by MacKinnon⁶¹ using the mediation package available in R.⁶² Specifically, we will use this approach to explore the potential role of changes in aerobic capacity, adherence to the DASH diet, and body weight as mediators that might explain a treatment effect. We also will examine potential moderators of treatment by testing interaction terms between treatment group and background characteristics. The moderators of primary interest are race, age, gender, presence of kidney disease or diabetes, BRS, and baseline levels of BMI and physical activity. In order to reduce the chance of a Type I Error, we will evaluate these interactions using a pooled 2 degree of freedom test using $p = .05$ as the criterion for statistical significance.⁶³ For the 1-year BP outcomes, we will use mixed models, incorporating the same covariates as in the primary analyses, but also including the immediate post-treatment and 1-year BP as repeated measures. All analyses will be carried out using SAS (Cary, NC) or R (<http://cran.r-project.org/>) software.

Power Analysis

The primary effect of interest is the treatment group difference in clinic SBP at 4 months. Power estimates were made based on the following specifications, based in part on our prior work with hypertensive adults¹³: 1) a general linear model for clinic SBP; 2) an initial sample size of 150 patients with 2:1 group allocation and 15% attrition at 16 weeks; 3) alpha of 0.05; 4) a standard deviation of 10.2 mm Hg for clinic SBP, and 13 mm Hg for the supportive ambulatory SBP outcome. For clinic SBP, we will have 80% power to detect about a 5.4 mm Hg group difference, and 90% power to detect about a 6.3 mm Hg difference. For ambulatory SBP, we will have 80% power to detect a group difference of about 6.9 mm Hg; at 90% power, we will be able to detect about an 8.1 mm Hg treatment difference. With respect to secondary biomarker endpoints (e.g., BRS, arterial stiffness) we will have 80% power to detect at least a 0.53 standard deviation difference between treatment groups on a given endpoint.

DISCUSSION

In order to make informed choices, patients and their providers need valid empirical evidence about the merits (or ‘demerits’) of structured lifestyle modification for patients with RH. Because the existing research is relatively sparse and was conducted primarily in unmedicated hypertension patients, it remains to be seen if patients with RH will be able to achieve significant lifestyle changes, and whether such changes will produce clinically significant improvements in BP control. It cannot be assumed that RH patients, who have complied with drug therapy yet failed to achieve target BP levels, will respond in the same way to lifestyle modifications as those who are not on medication. Patients who are refractory to medications may not achieve significant BP reductions from lifestyle changes, either. The value of lifestyle modification for RH patients remains an important and unanswered empirical question that needs to be examined in order to ascertain whether intensive, structured lifestyle interventions may be an effective treatment option for these patients. Indeed, the recently published American Heart Association and American College of Cardiology joint Guidelines on Lifestyle Management to Reduce Cardiovascular Risk noted that there is a lack of data on the effects of lifestyle modification in treated hypertension patients and identified this as being a priority area for future research.⁶⁴ If the

TRIUMPH lifestyle intervention proves successful in lowering BP and if the results are confirmed in subsequent studies, it could be argued that third-party payers should support the participation of patients with RH in CR programs.

Patients with RH are typically sedentary and obese,¹ so a lifestyle intervention including exercise, weight loss, and optimal nutrition has the potential to lower BP substantially. There is now good evidence that for behavior change to be successful, interventions should be linked to structured programs designed to facilitate behavior change.⁶⁵ To date, no RCT has tested an intensive, structured lifestyle intervention in patients who have uncontrolled BP despite being on 3 or more antihypertensive medications. Also missing from the research literature is an examination of “moderators” of lifestyle interventions. It is important to determine characteristics of patients who respond to lifestyle modifications so that interventions can be delivered to those most likely to benefit, and so that alternative strategies can be developed for those unlikely to respond. TRIUMPH will examine a variety of possible moderators as potential individual difference measures that could affect BP response to lifestyle modification.

In summary, TRIUMPH is a randomized clinical trial that will test the hypothesis that an intensive, 4-month, cardiac rehabilitation-based lifestyle modification program to promote exercise, the DASH eating plan, and weight loss will result in a meaningful decrease in BP, improvements in other biomarkers of CVD risk, and enhanced quality of life in patients with RH. Moreover, we will determine if lifestyle changes can be maintained for a year. The results of this study will inform patients, providers, and policy makers in judging whether structured lifestyle interventions may be an effective treatment option for individuals with hypertension that is refractory to medical therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

FUNDING SOURCE: Supported by a grant (HL122836) from the National Heart, Lung, and Blood Institute. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

ABBREVIATIONS

ABP	Ambulatory blood pressure
ARB	Angiotensin receptor blocker
BMI	Body Mass Index
BDI	Beck Depression Inventory
BP	Blood pressure
BRS	Baroreflex sensitivity
C-LIFE	Center-based lifestyle intervention

CO	Cardiac output
CVD	Cardiovascular disease
CR	Cardiac rehabilitation
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic blood pressure
DDD	Daily Defined Dose
EEG	Electrocardiogram
GFR	Glomerular filtration rate
hsCRP	High-sensitivity C-reactive protein
HR	Hazard Ratio
HRV	Heart rate variability
IVST	Interventricular septal thickness
ITT	Intent to Treat
LVEDD	left ventricular end-diastolic diameter
LVH	Left ventricular hypertrophy
MAP	Mean arterial pressure
PWT	Posterior wall thickness
PWV	Pulse wave velocity
QoL	Quality of life
RCT	Randomized clinical trial
RH	Resistant hypertension
SBP	Systolic blood pressure
SEPA	Standardized Education and Physician Advice
STAI	State-Trait Anxiety Inventory
SVR	Systemic vascular resistance

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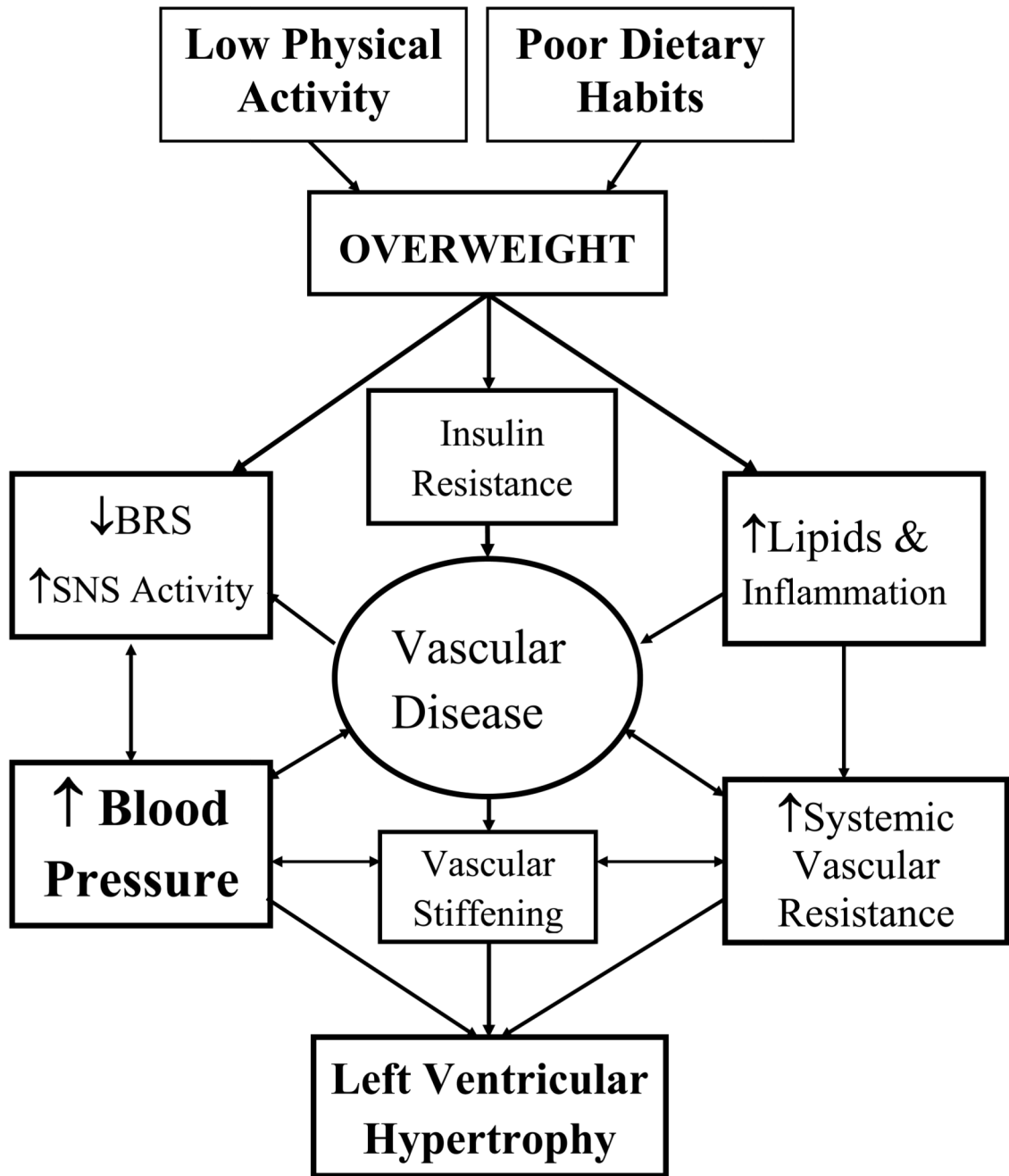


Figure 1. Conceptual Model

depicts a model by which poor dietary habits and lack of physical activity may adversely impact BP in this population, and how the complex interplay of autonomic, metabolic, inflammatory, cardiac, and vascular function may be both a cause and consequence of RH. The TRIUMPH study is designed primarily to evaluate whether an intensive lifestyle intervention delivered in a CR setting can achieve clinically significant BP lowering in patients whose BP has failed to be adequately controlled by the combined effects of at least

3 antihypertensive medications. It is also designed to provide insight into whether diet and exercise improve comorbid disease and associated biomarkers of CVD risk in RH patients.

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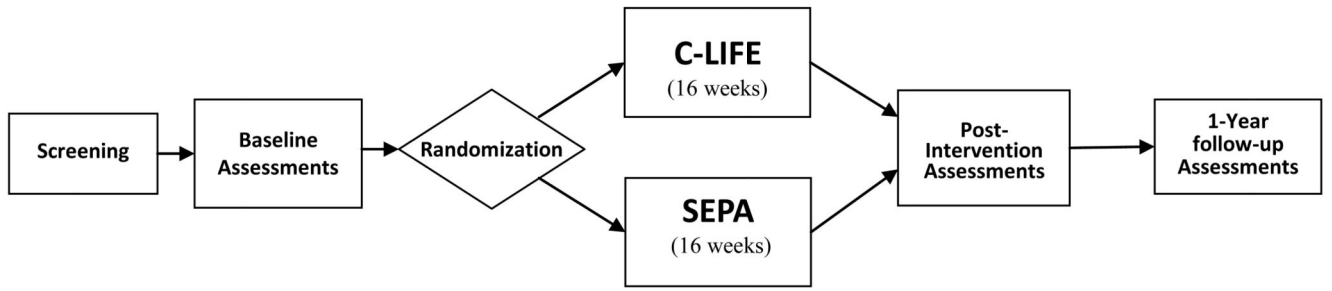


Figure 2. Study Design Overview

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Table 1

Study Outcomes, Assessment Methods and Schedule

Study Outcomes/ Endpoints	Assessment Methods	Timepoint
Clinical Outcomes		
Blood pressure	Automated BP monitor 24-hour ambulatory BP monitor	Screening, baseline, 4M, 12M Baseline, 4M, 12M
Body weight	Calibrated digital scale	Screening, baseline, 4M, 12M
Waist circumference	Tape measure	Baseline, 4M, 12M
Metabolic profile	Fasting serum glucose, insulin and lipids	Baseline, 4M, 12M
Neuroendocrine profile	Serum aldosterone, plasma renin activity, 24-hour urine catecholamines	Baseline, 4M
Kidney function	Serum creatinine Urine albumin and creatinine	Screening, baseline, 4M, 12M Baseline, 4M, 12M
Systemic inflammation markers	High-sensitivity C-reactive protein	Baseline, 4M
Cardiovascular Outcomes		
Left ventricular mass/geometry	Echocardiography	Baseline, 4M, 12M
Arterial Stiffness	Pulse wave velocity	Baseline, 4M, 12M
Baroreflex sensitivity	Finometer instrument	Baseline, 4M
Estimated CVD Risk	Framingham Risk Score	Baseline, 4M, 12M
Aerobic Capacity	Modified Balke exercise treadmill test	Baseline, 4M, 12M
Physical Activity	7-day accelerometer monitoring, Community Healthy Activities Model Program for Seniors Activity Questionnaire	Baseline, 4M, 12M
Dietary Intake	Automated Self-administered 24-hour recall, 24-hour urine sodium, potassium, and creatinine	Baseline, 4M, 12M
Psychosocial Outcomes		
Quality of Life	Short-form-36	Baseline, 4M, 12M
Depression	Beck Depression Inventory	Baseline, 4M, 12M
Anxiety	State-Trait Anxiety Inventory	Baseline, 4M, 12M
Self-esteem	Rosenberg Self-Esteem Scale	Baseline, 4M, 12M
Health Locus of Control	Health Locus of Control Scale	Baseline, 4M, 12M
Medication Adherence	Morisky Adherence Scale, <i>Medication Event Monitoring System</i>	Screening, baseline, 4M, 12M
Clinical Events	Interview, medical record adjudication	4M, 12M and annually up to 5 yrs

Study Outcomes/ Endpoints	Assessment Methods	Timepoint
All-cause mortality, non-fatal myocardial infarction, stroke, CV-related hospitalization, hypertensive emergency, CV procedure, doubling of serum creatinine or end-stage renal disease		

Note: BP= blood pressure; CV = cardiovascular; 4M= 4-months; 12M= 12-months.

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