Protocol
9/14/2021
NCT# 03295734

Project Title

ACES – Ace Inhibitors Combined with Exercise for hypertensive Seniors

Abstract:

The purpose of this project is to conduct a randomized, controlled trial (RCT) to determine if choice of antihypertensive medication influences changes in functional status and other cardiovascular risk factors among older persons with hypertension. Functional status, determined by measures of physical performance, is an important predictor of cardiovascular outcomes in older adults. Seniors with compromised function experience more CV events, have a higher risk of undergoing cardiac surgery and higher risk of CVD-related death than higher-functioning peers. Seniors with hypertension experience accelerated declines in function, and presently physical exercise is the primary strategy for preventing this decline. However, functional responses to exercise are highly variable and appear to be influenced by the type of antihypertensive medication(s) utilized to control blood pressure. Preliminary evidence suggests that, compared to other first-line antihypertensive agents, angiotensin converting enzyme (ACE) inhibitors enhance exercise-derived improvements in functional status among hypertensive seniors. This RCT will test this hypothesis. Sedentary men and women $\geq$ 60 years of age with functional limitations and hypertension will be recruited from three sites to participate in a 32 week intervention study. Participants will be randomly assigned to one of three first-line antihypertensive agents: (1) the ACE inhibitor perindopril, (2) AT1 receptor antagonist losartan, or (3) the thiazide diuretic hydrochlorothiazide. All participants will also participate in a structured aerobic exercise intervention. The primary aim is to determine if, compared to losartan and HCTZ, perindopril improves self-paced gait speed. The secondary aim is to determine the relative effect of perindopril on a) exercise capacity, b) body mass and composition, and c) circulating indices of cardiovascular risk. In exploratory analyses, skeletal muscle biopsies will be collected to evaluate the influence of study drugs on indices of skeletal muscle angiogenesis. This study is expected to differentiate beneficial effects of three FDA-approved antihypertensive medications on an emerging cardiovascular risk factor in a clinically-relevant population. Thus the study has important implications for expeditiously influencing clinical practice guidelines in the prescription of antihypertensive drugs to millions of Americans.

Background:

Cardiovascular disease (CVD) is the leading cause of death in the United States, and persons over 60 years of age account for over 80% of deaths attributable to CVD.[1] CVD is also the second leading cause of disability among older adults,[2]an important contributor to the loss of independence and subsequent institutionalization. As a consequence, older adults account for nearly three-quarters of health care expenditures related to CVD.[3] Importantly, these expenditures are expected to increase dramatically in coming years as the number of older adults is expected to double to approximately 80 million in the next three decades.[4] This aging of the American population predicts massive burden in terms of clinical and economic costs related to CVD. Consequently, the identification of interventions capable of reducing CVD risk among older adults is an important goal with dramatic public health implications.

The loss of functional abilities in advanced age is associated with not only the onset of disability and the loss of independence but also with increased rates of cardiovascular morbidity and mortality.[5-7]Declines in self-paced walking speed, a recommended indicator of health and well-being among seniors,[8,9] is also associated with incident stroke,[10] adverse outcomes following cardiac surgery,[11] as well as cardiovascular and all-cause mortality.[6,7,12] Compared to normotensive counterparts, older persons with hypertension experience accelerated declines in walking speed [13,14] and increased rates

of disability.[15,16] We also observed this phenomenon in the Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) study. Seniors with hypertension who were given a control intervention had slower long-distance walking speeds at baseline ($p < 0.001$) and experienced gait slowing that was not observed in normotensive persons.

Currently, physical exercise is the standard intervention for improving physical function among older adults. Indeed, several studies have demonstrated the beneficial effects of exercise programs on the function of older adults.[17-20] We also recently demonstrated the general efficacy of exercise training in improving the functional status of moderately-impaired seniors in LIFE-P.[21] However despite the global benefit of the exercise program on the functional status of the study population, these benefits did not extend to a large proportion of individuals. Improvements in functional measures observed in response to exercise were driven largely by persons using ACE inhibitors[22] – despite the fact that this group accounted for approximately one quarter of the study population. Indeed, persons not using ACE inhibitors displayed relatively poor functional adaptations to exercise.

ACE inhibitors lower blood pressure by blocking the conversion of angiotensin I (ANG I) to angiotensin II (ANG II) and inhibiting the degradation of bradykinin, a potent vasodilatory substance. However, some therapeutic effects of ACE inhibitors may be mediated by mechanisms that are independent of blood pressure regulation. Proposed pleiotropic effects of ACE inhibitors include reducing reactive oxygen species production, anti-inflammatory properties, and reducing myocyte hypertrophy and fibrosis.[23] In high risk patients enrolled in the Heart Outcomes Prevention Evaluation (HOPE) trial, most of the benefit of ramipril compared to placebo appeared to be unrelated to blood pressure lowering.[24] Moreover, three trials in patients with hypertension and type 2 diabetes,[25-27] suggested that, for the prevention of cardiovascular events, ACE inhibitors were superior to other drugs, despite minimal differences in blood pressure levels. We also reported similar results in a meta-analysis extended to all patients with hypertension.[28]

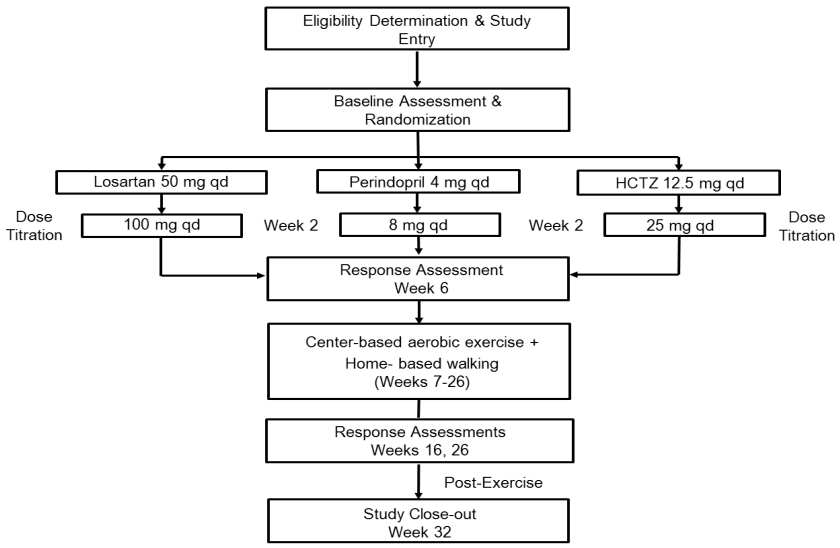
In recent years, ACE inhibitors have been purported to attenuate declines in functional status among seniors.[29,30] Epidemiologic evidence from the Women's Health and Aging Study (WHAS) and the Systematic Assessment of Geriatric drug use via Epidemiology (SAGE) study indicated that, compared to non-users, seniors using ACE inhibitors displayed attenuated declines in walking speed and limitations in Activities of Daily Living (ADL).[31,32] Despite this promising evidence, the benefits of ACE inhibitors on functional outcomes appear to be limited when utilized as an isolated treatment.[22,33,34] However, our preliminary evidence suggests that these benefits may be manifest when combined with exercise. We previously reported retrospective findings suggesting that older persons who took ACE inhibitors had greater exercise-derived improvements in functional status than non-users.[22] As a result of these findings and other pre-clinical and epidemiological findings from our group,[31,35-37] we developed our central hypothesis that – compared to other first line antihypertensive therapies – ACE inhibitors enhance functional responses to exercise among hypertensive seniors. We then conducted a pilot RCT to refine the study protocol and demonstrate the safety and feasibility of conducting the study interventions in the target population. The objective of this project is to conduct a fully-powered RCT to test our central hypothesis.

Specific Aims:

We propose to compare, when combined with chronic exercise, the effects of the ACE inhibitor perindopril to those of an AT1 receptor antagonist (losartan) and an alternative first-line antihypertensive that functions independent of the renin-angiotensin system (hydrochlorothiazide). We will recruit hypertensive seniors with functional limitations (N = 213) from two geographically distinct sites and follow them for 32 weeks. Participants (n = 71/group) will be randomly assigned to receive, in a triple-masked fashion, either perindopril (dose titrated to a maximum of 8 mg/day), losartan (maximum 100 mg/day) or HCTZ (maximum 25 mg/day). All participants will also engage in a 20-week structured exercise program (150 min/week of aerobic exercise) preceded and followed by 6-week observational periods. The specific aims are to:

PRIMARY AIM. Determine if, compared to losartan and HCTZ, perindopril improves the primary outcome of short distance (4m) self-paced gait speed, a key predictor of cardiovascular outcomes in seniors.[10-12,39-41]

SECONDARY AIM. Determine the relative effect of perindopril on the following secondary outcomes: (1) exercise capacity, defined by distance covered during a maximal 6-minute walk test, (2) body mass and composition, measured by DEXA, (3) clinical measures of cardiovascular risk, e.g. glucose, cholesterol, hsCRP, (4) systemic and vascular inflammation, e.g. TNF-α, IL-6, VCAM-1, E-selectin, and (5) circulating indices of oxidative stress, e.g. oxLDL, MPO.



Scheme 1. Overview of Study Design.

EXPLORATORY AIM. Assess the effects of study drugs on exercise-induced changes in indices of skeletal muscle angiogenesis, including 1) the proportion of type I (oxidative) muscle fibers, 2) capillaries per muscle fiber, and 3) muscle content of mRNA and proteins related to angiogenesis.

Research Plan:

We propose to conduct a randomized, triple-masked trial to evaluate the efficacy of combining physical exercise with ACE inhibitor use as a strategy to improve functional status and other cardiovascular risk factors among older persons with hypertension. We will recruit 107 adults over 60 years of age with hypertension and randomly assign them to daily use of one of three first-line antihypertensive medications: 1) the ACE inhibitor Perindopril, 2) the ARB Losartan, or 3) the thiazide diuretic Hydrochlorothiazide (HCTZ). All participants will also engage in a 20 week structured exercise intervention. The total intervention period will be 32 weeks and separated into 3 phases: Pre-exercise observation (weeks 1-6), exercise intervention (weeks 7-26), and post-exercise follow-up (weeks 27-32).

STUDY POPULATION.

Inclusion criteria	Exclusion criteria
• Age 60 years and older • Hypertension – untreated (SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg) or treated • > 290 seconds needed to complete long-distance corridor walk test, as an indicator of functional limitation and moderate to low aerobic fitness[7] • Sedentary lifestyle, defined as <150 min/wk of moderate physical activity as assessed by CHAMPS questionnaire[42] • Willingness to participate in all study procedures, including allowing study team to communicate with primary care physician regarding changes in antihypertensive treatment	• Resistant hypertension, defined as BP > 140/90, despite the use of three or more anti-hypertensive drugs[43] • SBP > 180 mm Hg or DBP > 110 mm Hg • Chronic kidney disease • Serum creatinine >2.5 mg/dL in men or >2.0 mg/dL in women • Serum potassium exceeding the laboratory reference • Urinary protein > 1 on dipstick • Abnormal liver enzymes (AST, ALT, or alkaline phosphatase > 2.5 times the upper limit of normal) • Severe cardiac disease, including NYHA Class III or IV congestive heart failure, clinically significant aortic stenosis, history of cardiac arrest, use of a cardiac defibrillator, or uncontrolled angina • Subjective or objective indicators (ECG) of ischemic heart disease (e.g., angina, ST segment depression) or serious arrhythmias at rest without follow-up evaluation Significant cognitive impairment, defined as a known diagnosis of dementia or a Mini-Cog™ score < 3;

	• History of hyponatremia with use of HCTZ • Simultaneous participation in another intervention trial • Known hypersensitivity to ACE inhibitors (exclusion only to ACEi arm; will be randomized among other two interventions)

RECRUITMENT. We will develop a targeted recruitment approach based on previous experiences utilizing methods of recruitment that include direct mailings, newspaper classified and print ads, community luncheons and health fairs, as well as clinic referrals. Our group has been extremely successful in implementing this approach in past studies.

SCREENING AND STUDY ENTRY. Participants deemed eligible based on an initial phone screening will be encouraged to consult with their physician and invited to an in-person screening visit. If all study entry criteria are met, participants will be scheduled to return to the clinic for baseline assessments. Randomized participants will be followed with clinic visits for a total follow-up duration of 32 weeks following randomization. In addition to the screening visit, participants are required to attend the clinic for 6 assessment visits which includes a final close-out visit 6 weeks following the completion of study interventions. The assessment schedule is provided below.

PRIMARY AND SECONDARY OUTCOMES.

Outcome	Explanation
Gait speed (Primary)	Declining gait speed in late-life is associated with increased risk of numerous cardiovascular outcomes,[7,10-12] and has been proposed as a novel cardiovascular screening outcome in older adults due to its high prognostic capacity, high reproducibility, and extraordinary cost-effectiveness.[44,45] We will assess gait speed by asking the participants to walk at their usual pace over a 4 m course.
Exercise Capacity	We will assess exercise capacity of participants using the six-minute (6-min) walk test, a safe and reliable test of aerobic endurance in older persons and those with cardiovascular conditions.[46,47] This test has strong reproducibility, with intra-subject coefficients of variation averaging < 10%, and has a modest correlation with peak VO_2.[48] Participants will be asked to walk as far and fast as possible for 6-min on a 40 m track. Participants will be allowed to use their customary walking aids and to rest if required.
Body Composition	Body composition is a critical cardiovascular risk factor and a primary contributor to exercise capacity and overall functional status. We will assess body composition by measuring whole-body fat percentage (BF%) as well as central adiposity (lumbar region) using dual x-ray absorptiometry.
Circulating indices of cardiovascular risk	In addition to measurement of clinical safety parameters, fasting blood samples (serum or plasma as appropriate) will be sent to Quest Diagnostics for clinical laboratory evaluation of blood lipids, glucose, and hemoglobin A(1c) levels. Samples will also be assayed for prominent markers of inflammation (e.g. TNF-α, IL-6, VCAM-1, E-selectin) and oxidative stress(e.g. oxidized LDL and myeloperoxidase). Assays will be performed using previously-utilized, commercially-available ELISA kits.

EXPLORATORY OUTCOMES. Skeletal muscle biopsies will be collected at baseline and 26 weeks from a subset of participants. Participation in the biopsy will be voluntary, thus unwillingness to participate in the biopsy will not preclude them from participating in the trial. Biologics analyses of skeletal muscle samples will prioritize analyses related to angiogenesis given the finite amount of tissue obtained. Remaining tissue will be saved to evaluate other possible biologic mechanisms of interest including mitochondrial function, inflammation, and glucose metabolism. Skeletal muscle immunohistochemistry (i.e. fiber typing/capillarization) will be performed as published.[49] Skeletal muscle content of mRNA and protein related to angiogenesis – including vascular endothelial growth factor (VEGF), VEGF receptor 2, hypoxia inducible factor 1α, and nitric oxide isoforms 1-3 – will be measured by Q-PCR and western blotting as published.[49-51]

SUPPORTIVE OUTCOMES. In addition to the measures proposed in the aims, we will also evaluate a select group of supporting measures that will aid in the interpretation of study outcomes. These measures will include co-morbidity, diet, physical performance via the Short Physical Performance Battery (SPPB), and objective monitoring of daily physical activity via accelerometry. Co-morbidity will

be evaluated using the Charlson Index.[52] Dietary habits will be evaluated using NIH Quick Food Scan Questionnaire Physical activity will be measured using a hip-worn physical activity monitor as published previously.[54] Additionally, participants volunteering for the biopsy portion of the study will also be asked to complete a treadmill-based test of aerobic fitness to determine maximal ventilatory capacity.

DATA COLLECTION SCHEDULE.

Data collection summary by study visit

Study Phase	Pre-randomization		Pre-Exercise		Exercise		Post-Exercise
Visit description (FU=follow-up, CO= close-out)	Screen	Baseline	Dose Titration	FU	FU	FU	CO
Visit number	1	2	3	4	5	6	7
Week number	-2	0	2	6	16	26	32
Informed consent, review inclusion/exclusion criteria	x						
Personal interview, medical history, medication use	x						
Office blood pressure (sitting + standing), vital signs	x	x	x	x	x	x	x
Anthropometry, ECG, Physical Exam	x						
Functional measures for screening	x						
Blood and urine for safety labs	x		x	x	x	x	
Randomization		x					
4 m walk, 6 minute walk, blood for study assays		x		x		x	x
DEXA, Short Physical Performance Battery		x				x	
Dispense study medications		x	x		x		
Collect home BP monitor data			x	x	x	x	x
Collect supportive outcome measures		x		x		x	x
Assess adverse experiences			x	x	x	x	x

RANDOMIZATION. Study randomization will be performed by using a randomization scheme provided by the study biostatistician. The randomization scheme will be concealed to investigators and study staff until the completion of the study.

PHARMACOLOGIC INTERVENTION. Eligible participants will be randomly assigned to one of the three study medications. Blood pressure will be controlled according to published hypertension guidelines.. Participants assigned to Perindopril will be given an initial dose of 4 mg/day for two weeks after which, pending approval of the study medical safety officer, the dose will be increased to 8 mg/day. If the 4 mg/day dose controls blood pressure to ≤120/≤80 or the low dose is not tolerated due to issues such as hypotension, cough, or hyperkalemia, the participant will be given the lower tolerated dose. The same scheme will be utilized for the Losartan group (dose titrated from 50 mg/day to 100 mg/day) and the HCTZ group (12.5 mg/day to 25 mg/day). ***Note: Participants with a prior history of adverse experiences to ACE inhibitors will be randomly assigned to either Losartan or HCTZ.***

The study clinician also has the discretion to immediately start the participant at the higher dose should it be warranted to safely manage the participant's blood pressure. It is possible that participants may need > 1 drug to control blood pressure after receiving the full dose of study drug. In this case, amlodipine will be used for each group as it is a good combination agent and does not cause bradycardia. If needed, amlodipine can be given at 2.5, 5 or, 10 mg/day. The proportion of each study arm requiring amlodipine will be determined and evaluated in sensitivity analyses when interpreting study data. Participants requiring additional medications to control blood pressure will be removed from the study, though we envision this scenario as unlikely based on our entry criteria and experience in our pilot study. Because of the effects of HCTZ on potassium, it is also possible that some participants may require potassium supplementation in addition to the study medication. Serum potassium will be evaluated at study assessment visits and oral potassium chloride will be prescribed for any serum potassium <3.5 mEq/L. Serum potassium will then be rechecked (in addition to regular study visits) every 2-3 weeks with potassium doses increased as needed until potassium is normalized.

If participants are interested and their primary care physician recommend continuing the assigned randomized study medication, the physician's office can choose to complete the study medication information request form faxed directly to the site institution investigational drug service (keeping the study investigative team masked to assignment). On this form, the investigational drug service will identify the study medication and dose assigned and send it directly back to the requesting primary care physician office after all participation in study visits have ended in an a HIPAA-compliant manner. The medication disclosure would not happen until after final data collection, and participants would be provided with additional study drug to continue for a short period until receiving medication filled from their physician.

DRUG PREPARATION. Study drugs will be provided by the Research Pharmacy which provides medications specifically for pharmacologic research studies. Study drugs will be placed in standard prescription medication receptacles large enough to supply the drug until the next study visit. The receptacles will be labeled with vital study information such as the study name, study week number, date of preparation, and study team contact information. The study coordinator will communicate with the Research Pharmacy prior to each patient follow-up visit to assure uninterrupted provision of study drug.

EXERCISE INTERVENTION. In addition to taking the study drug, all participants will engage in a 20 week structured exercise intervention. The intervention will include twice weekly, center-based, aerobic exercise as well as home-based walking. This intervention is designed to achieve a total of 150 minutes of aerobic activity per week, meeting clinical and public health guidelines for the general public,[55] older persons,[56-58] and those with hypertension.[59]

Each center-based session will begin with a brief warm-up followed by moderate-intensity treadmill walking. Other forms of endurance activity (e.g., stationary cycling) may also be utilized. Participants will be introduced to the intervention exercises in a structured way such that they begin with lighter intensity and gradually increase during the first weeks of the intervention. According to ACSM/AHA guidelines,[56] exercise intensity will be monitored using a subjective 0-10 scale for physical exertion (Borg CR10 scale).[60] Participants will initially be instructed to exercise at a moderate intensity, equivalent to a 5-6 on the CR10 scale. During each exercise session, participants will also be asked to wear a heart rate monitor to measure mean pulse during their sessions. Pulse measurement will allow interventionists to help participants with gauging the accuracy of their subjective ratings and promote safety. After the initial two weeks of activity, participants will be asked to exercise at a target intensity of 70-80% of predicted maximal heart rate (220 – age). Walking/Cycling distance and grade will also be monitored during each session and participants will be encouraged to increase the distance and grade exercised each session. For home-based activity, participants will be encouraged to perform walking at a moderate intensity throughout the duration of the study. They will also be asked to wear a commercially-available fitness monitor throughout the study period to monitor home-based activity.

STATISTICAL ANALYSIS PLAN. The primary outcome for the study will be change in 4m gait speed from week 6 to 26 (the exercise period) in the trial. Prior to all analyses, the assumption of normality will be checked using histograms and normal probability plots. For gait speed, we will use linear mixed effects models with random intercept to account for the temporal correlation among the multiple observations for each subject. Follow-up model-based contrast tests will be applied to test the effect of perindopril compared to losartan and HCTZ. For all the secondary outcomes other than body mass and composition, we will fit similar linear mixed effects models as for the primary outcome. For the body mass and composition measures, we will use the analysis of covariance (ANCOVA) method. Exploratory outcomes will also be evaluated using ANCOVA. Corrections for multiple comparisons will be utilized within (e.g., four serum inflammatory analytes) but not between (i.e., exercise capacity vs. body composition vs. serum analytes) secondary and exploratory outcomes. For all outcomes, the primary analysis will include data from all randomized participants, in line with intent-to-treat principles. A secondary analysis will be performed to evaluate changes during the full intervention period (weeks 0–32). For each analysis, sensitivity analyses will be performed to evaluate the impacts of relevant potential confounders including age, sex, race, site, retention (i.e., drop-out), adherence (i.e., medication and exercise). Given that those with cough history cannot be randomized to ACE, additional

sensitivity analyses will be performed on just those without cough history to examine the robustness of the primary and secondary analyses based on all randomized patients.

SAFETY MONITORING PLAN. Safety of participants is our primary concern. Prior to study entry, prospective participants will be advised to consult with their physician. Numerous safety procedures will be utilized to insure participant safety. These strategies have proven successful in minimizing adverse events in large-scale trials from our group of both exercise[21] and antihypertensive drug use.[61] First, many of the exclusion criteria are designed to exclude those at moderate to high risk. Participant education about safety begins with the consent process and continues throughout the study. Potential adverse events for study related activities and interventions are explained to each participant by trained study personnel during the informed consent process. Participants will be encouraged to notify study staff immediately if they have any adverse experiences that could be related to the study drug or their BP management. The dose titration and physician monitoring of BP and clinical chemistries are in place to minimize adverse responses to the study drugs. Abnormal symptoms or vital signs detected during intervention visits will be discussed with the study physician in real time, who will dictate the appropriate course of action. Study staff will also inform the participant's primary care physician of the participant's initial enrollment in the trial, as well as of all changes in medication prescription during their participation in the trial. Participants will be provided with a copy of the letter sent to their physician. They will also be provided with a wallet size card containing study details and contact information.

In addition, subjects will be provided a home blood pressure monitor and encouraged to conduct daily blood pressure monitoring. We will provide participants with a home BP monitor that meets the standards of the British Society of Hypertension and the Association for the Advancement of the Medical Instrumentation.[62] This device utilizes a triplicate mode of measurement and averages the values, to closely resemble clinical measurements. The device records and stores SBP, DBP, HR, and a date/time stamp which are downloadable via a computer interface. Participants will be instructed to take their home BP three times daily, on rising from bed, midday and before retiring. Participants will be instructed to report any SBP > 180 or < 90 mmHg or DBP > 100 or < 60 mmHg to the study coordinator immediately. Those with two or more such pressures will be scheduled immediately for a clinic visit, at which time it will be determined whether the patient is taking the home BP properly. Blood pressure will also be monitored at each assessment visit in the clinic. Participants will be withdrawn from the study at the discretion of the study clinician for any DBP > 100 mmHg or SBP > 180 mmHg, and will be automatically removed from the study for any weekly average home BP above these thresholds. The cardiologist may decide to exclude subjects with slightly lower BP levels than these cut points, but for whom there is any medically-relevant concern that would preclude continued participation. Withdrawn participants will be returned to their standard antihypertensive therapy under the supervision of their physician or referred for care.

If study treatments according to the scheduled protocol do not manage hypertension safely, the study clinician has full discretion to manage the antihypertensive regimen to ensure safety. He can be un-blinded to study medication randomization at any time to ensure proper care. If abnormal BP readings or lab values are identified, he may alter antihypertensive regimen as appropriate by either altering the dose of study medication, adding other antihypertensive drugs or supplements (e.g. potassium) to the drug regimen, or withdrawing the participant from the study medication and returning to pre-study therapy. When unblinding is required, the PI or designee will contact the study pharmacy which will send the information regarding medication the participant is taking directly to the cardiologist who will take the appropriate medical steps. In cases where the study team learns about a serious adverse event or medical emergency, the study clinician will be immediately informed. Unblinding procedures will be the same as described above. In cases of emergency, non-study medical personnel treating the participant will also be provided with study drug and dosage information as necessary to ensure proper care. The participant's primary care physician will also be notified of the emergency event.

Clinical chemistry indicators – e.g. creatinine, sodium, potassium, and urinary albumin – will be also monitored at all study visits. The study clinician can elect to replace potassium at any value, with protocol mandated prescription of oral potassium chloride for any potassium <3.5 mEq/L. If adverse

serum potassium values are noted, serum potassium will be rechecked (in addition to regular study visits) every 2-3 weeks with potassium doses increased as needed until potassium is normalized. If other adverse clinical responses occur, e.g. hyperkalemia or hyponatremia, the dose of study drug will be adjusted appropriately by the study clinician. Serious and non-serious adverse experiences will be monitored at each study visit and as reported. Interventionists will also monitor adverse events as they are reported as well as any potential events that occur during performance of the exercise intervention.

Center-based assessments and interventions will be conducted and supervised by trained staff who will monitor potential adverse experiences and symptoms. All assessors and interventionists receive CPR training and training on management of acute events including syncope, chest pain, acute dyspnea, focal neurological symptoms and abnormal vital signs. Portable defibrillators are available and all study staff have on-call access to the study physician and contact numbers for emergency services are. Institutional and community EMS services will be activated if needed. As indicated previously, participants will be taught the importance and proper method of warming-up prior to and cooling-down following structured activity sessions. If at any point during an exercise session, participants develop chest pain, shortness of breath, or dizziness, they will be instructed to rest and to contact the center and their physicians if these symptoms persist or recur with further exercise. Blood pressure and heart rate will be measured before and after the training session at each center. Physician clearance will be required prior to returning to exercise for participants experience any of the following during a previous exercise session: decrease in diastolic blood pressure $\geq$ 20 mm Hg during the activity, increase in systolic blood pressure to $\geq$ 200 mm Hg or in diastolic blood pressure $\geq$110 mm Hg in response to activity, increase in heart rate $\geq$ 90% of age predicted maximum, unusual or severe shortness of breath, chest pain or discomfort, palpitations, light headedness, dizziness or feeling about to faint, or a session had to be discontinued because of other medical symptoms, excluding musculoskeletal symptoms (e.g., knees, ankles, hips), reported by the participant.

Any significant adverse events will be reported promptly to the IRB and to the Data Safety Monitoring Board (DSMB). Again, written informed consent will be obtained after explanation to subjects about all procedures and time commitments. The study interviewers will explain to prospective participants the purpose, methods and extent of the study. Potential participants will be asked to read the informed consent form and to ask questions. The form will be written in simple, easy-to-understand language. Staff members will also review all key aspects of the study verbally. Confidentiality of data will be maintained by using research identification numbers that uniquely identify each individual. Data will be used only in aggregate and no identifying characteristics of individuals will be published or presented. Finally, the study protocol has been registered at www.ClinicalTrials.gov (NCT# 03295734) and will be updated as required.

Possible Discomforts and Risks:

Potential risks are those associated with health information privacy, venipuncture, treatment with the antihypertensive agents, radiation from DEXA, and participation in exercise training and testing.

Venipuncture can be associated with pain, bruising, hematoma formation, superficial phlebitis, and rarely cellulitis or fainting.

Risks of antihypertensive drug therapy include the development of symptomatic orthostatic hypotension, postprandial hypotension, and syncope or falls. Specific risks of perindopril include hyperkalemia, cough, headache, weakness, dizziness, diarrhea, stomach pain, and upset stomach. Serious, but infrequent, risks include swelling, difficulty swallowing, lightheadedness, fainting, fever, sore throat, and irregular heartbeats. Risks associated with losartan include dizziness, leg, knee, or back pain, muscle cramps or weakness, diarrhea, and heartburn. Serious but less frequent risks include swelling, difficulty breathing/swallowing, and chest pain. Risks associated with diuretics, including HCTZ, include electrolyte imbalances (most notably hypokalemia, but could include hyponatremia, hypomagnesemia, and hypochloremia), increases in fasting blood glucose, muscle weakness, dizziness, cramps, extreme thirst, stomach pain, nausea, vomiting, diarrhea, loss of appetite, headache, hair loss, and gout. More serious risks include sore throat with fever, unusual bleeding or bruising, severe skin rash, and difficulty

breathing or swallowing. Notably, these drugs are FDA approved and widely utilized as therapies for hypertension among older adults. Significant attention will be paid to the monitoring of blood pressure, serum electrolytes and liver enzymes, and related adverse events to minimize risks associated with antihypertensive drug use.

The risk of radiation exposure from the 2 DEXA scans is very low. The radiation exposure from the 2 scans is equal to about 6 millirems, which is comparable to about 4 to 6 days of natural background radiation to which people in the United States are exposed to during their lives. The risk from this radiation exposure is considered to be low when compared to other every day risks.

The primary risk associated with moderate-intensity exercise training is skeletal muscle soreness. There are also other risks that relate to soft tissue injury, falls and fractures, exacerbation of arthritis and other joint conditions, post-exercise hypotension, and cardiovascular events. There is a risk that a participant may trip, stumble, or fall during the physical performance tests and experience shortness of breath, dizziness, palpitations, chest pain or discomfort, heartburn, light headedness, or feeling about to faint during the six min walk test.

Possible Benefits:

Importantly, the proposed project will have direct, tangible benefits for participants. These benefits include information about their health and assessments of their functional status. All study participants will be encouraged to communicate the results from the study to their primary care providers. Moreover, all participants – regardless of randomized group – will receive supervised exercise training and instruction about how to maintain exercise habits at home. We expect that these benefits will improve quality of life for all participants.

Conflict of Interest:

There are no conflicts of interest to report.

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