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Multi-modal intervention to reduce cardiovascular risk among hypertensive older adults: Design of a randomized clinical trial

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ABSTRACT

Persons aged over 65 years account for over 75% of healthcare expenditures and deaths attributable to cardiovascular disease (CVD). Accordingly, reducing CVD risk among older adults is an important public health priority. Functional status, determined by measures of physical performance, is an important predictor of cardiovascular outcomes in older adults and declines more rapidly in seniors with hypertension. To date, physical exercise is the primary strategy for attenuating declines in functional status. Yet despite the general benefits of training, exercise alone appears to be insufficient for preventing this decline. Thus, alternative or adjuvant strategies are needed to preserve functional status among seniors with hypertension. Prior data suggest that angiotensin converting enzyme inhibitors (ACEi) may be efficacious in enhancing exercise-derived improvements in functional status yet this hypothesis has not been tested in a randomized controlled trial. The objective of this randomized, double-masked pilot trial is to gather preliminary efficacy and safety data necessary for conducting a full-scale trial to test this hypothesis. Sedentary men and women ≥65 years of age with functional limitations and hypertension are being recruited into this 24 week intervention study. Participants are randomly assigned to one of three conditions: (1) ACEi plus exercise training, (2) thiazide diuretic plus exercise training, or (3) AT1 receptor antagonist plus exercise training. The primary outcome is change in walking speed and secondary outcomes consist of other indices of CV risk including exercise capacity, body composition, as well as circulating indices of metabolism, inflammation and oxidative stress.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in the United States, and persons over 65 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]. Thus the clinical and economic costs related to CVD are expected to increase dramatically in coming years. Consequently, the identification of interventions capable of reducing CVD risk among older adults is an important goal with dramatic public health implications.

Functional status, determined by measures of physical performance, is an important predictor of cardiovascular outcomes in older adults. Functionally-limited older adults, i.e. those with physical limitations which limit their ability to perform daily activities (e.g. low muscle strength, impaired gait), experience more cardiovascular events, have a higher risk of undergoing cardiac surgery and higher risk of cardiovascular-related death than higher-functioning peers [5–10]. Declines in self-paced walking speed, a recommended indicator of health and well-being among seniors [11,12], are also associated with incident stroke [6], adverse outcomes following cardiac surgery [8], as well as cardiovascular and all-cause mortality [5,10,13]. Compared to normotensive counterparts, older persons with hypertension experience accelerated declines in functional status [14–17]. Among older persons enrolled in the Charleston Heart Study, higher systolic blood pressure was associated with greater declines in functional outcomes and seniors with hypertension were at increased risk of developing new disability

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[14]. Hypertension was also associated with accelerated declines in walking speed among seniors participating in the Cardiovascular Health and Three-City studies [15,17]. Thus, older adults with hypertension represent a particularly high risk group for functional decline and associated cardiovascular events.

Accumulating evidence suggests that the choice of antihypertensive medication may play an important role in the rate of functional decline among older adults. 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 angiotensin converting enzyme (ACE) inhibitors displayed attenuated declines in walking speed and limitations in Activities of Daily Living (ADL) [18,19]. However, the results of subsequent randomized controlled trials (RCTs) were mixed, with studies reporting that ACE inhibitors may [20,21] or may not [22,23] improve functional status. While it remains possible that the efficacy of ACE inhibitors as a therapeutic for physical function may vary by drug and/or patient population, recent evidence from our group suggests that the greatest benefit of ACEi may be observed when combined with regular physical exercise [24,25] though a conflicting report exists [26]. This study was designed to begin to test our central hypothesis among older adults with hypertension that – compared to other first-line antihypertensive therapies – ACE inhibitors improve functional status and other cardiovascular risk factors when combined with regular exercise. The objective of this randomized pilot trial is to refine and finalize elements critical to conducting a future, fully-powered randomized, controlled trial to definitively test our central hypothesis.

2. Study design/methods

2.1. Overview

The study is a three-arm randomized, double-masked pilot trial among older, hypertensive men and women with functional limitations. All participants are assigned to participate in a structured exercise intervention while also being randomly assigned to one of three first-line antihypertensive medications for blood pressure management at target pressures of <140 mm Hg (systolic) and <90 mm Hg (diastolic). Study medications are ACE inhibitor perindopril, the AT1 receptor antagonist losartan, and the thiazide diuretic hydrochlorothiazide. Participants are followed for a period of 24 weeks to evaluate changes in study outcomes indicative of functional status and cardiovascular risk. Study assessments are conducted by blinded research staff during clinic visits at baseline, as well as 2-, 8-, 16-, and 24-weeks post-randomization (Fig. 1). Randomization and dispensing of study medications are conducted by an academic health center investigational pharmacy. Participant safety is overseen by a comprehensive study team — including the principal investigator, study cardiologist, study geriatrician, study staff, and an appointed Data and Safety Monitoring Board. The study is registered at www.clinicaltrials.gov prior to participant recruitment (NCT01891513) and all participants provide written informed consent based on documents approved by a university Institutional Review Board.

2.2. Participants

The study team is recruiting up to 72 (n = 24/group) functionally-limited older men and women with hypertension. Eligible participants are community-dwelling persons ≥65 years of age with a sedentary lifestyle, objective signs of functional limitations, as well as untreated hypertension or known uncomplicated hypertension. Persons with a primary indication for ACE inhibitor use, congestive heart failure (CHF), or coronary heart disease (CAD) are excluded. Persons with a known hypersensitivity to ACE inhibitors, with absolute contraindication(s) to exercise training according to American College of Sports Medicine guidelines [27] (e.g. unstable angina, uncontrolled cardiac dysrhythmias causing symptoms or hemodynamic compromise, symptomatic severe aortic stenosis, uncontrolled symptomatic heart failure) or with other

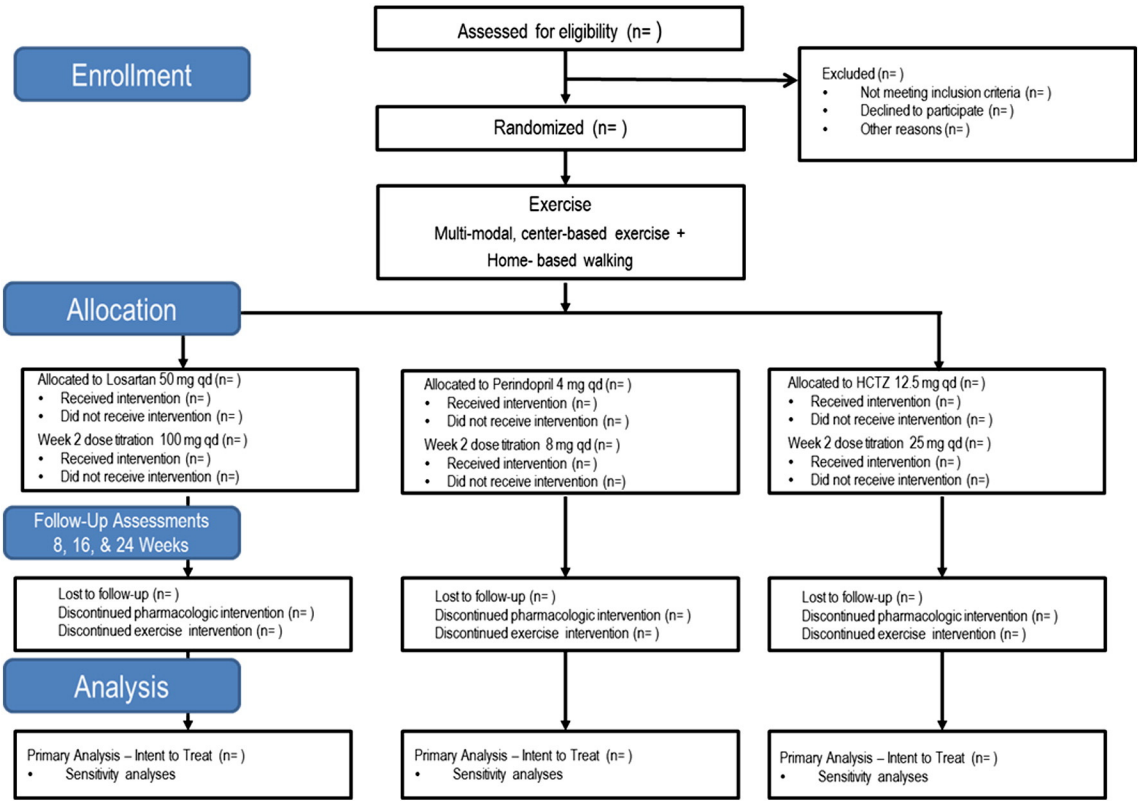

Fig. 1. Overview of study design according to CONSORT format.