Intensive Versus Standard Blood Pressure Lowering to Prevent Functional Decline in Older People

NCT01650402

Protocol

IRB Approval Version 4/16/2018

IRB Review
IRB NUMBER: IE-11-155S-2
IRB APPROVAL DATE: 04/16/2018

PROTOCOL TITLE:

INFINITY: Intensive versus Standard Blood Pressure Lowering to Prevent Functional Decline in Older People

Principal Investigators:

William B. White, MD, Calhoun Cardiology Center

Leslie Wolfson, MD, Department of Neurology

University of Connecticut Health Center, Farmington

Supported by:

The National Institute on Aging

2R01AG022092-06A1

TABLE OF CONTENTS

Page

I. Procedures Schedule

II. Informed Consent Form (approved by UCHC IRB June 2011)

III. Other *(add as many appendices as necessary)*

PARTICIPATING STUDY SITES

This is a single-site trial, taking place at the University of Connecticut Health Center, located at 263 Farmington Avenue in Farmington, Connecticut.

PRÉCIS

Study Title

Intensive versus Standard Blood Pressure Lowering to Prevent Functional Decline in Older People

Objectives

The goal of this randomized clinical trial is to determine if lowering and maintaining 24-h ambulatory systolic BP (ABP) to ≤130 mmHg (*intensive control*) versus <145 mmHg (*standard control*) slows/halts progression of deterioration of mobility and cognitive function linked to white-matter disease (also known as white-matter hyperintensity or WMH) in patients with normal or mildly impaired mobility and cognition in subjects with detectable cerebrovascular disease (≥0.5% WMH fraction of intracranial contents).

Design and Outcomes

The study is a single-site, prospective randomized, open-label trial with blinded endpoints (PROBE), in patients ages 75 and older with elevated 24-h systolic BP (>150 mmHg in the untreated state) who do not have unstable cardiovascular disease, congestive heart failure or history of stroke.

The key primary and secondary outcomes in the trial are:

1) change from baseline in mobility parameters (self-paced walk and stance times)
2) change from baseline in cognitive function (executive function, processing speed

3) Accrual of WMH over the course of the trial (36 months) including degeneration of tissue and tissue perfusion using an MRI technology known as diffusion tensor imaging (DTI)

Interventions and Duration

The study patients will be enrolled and randomized to one of two levels of ambulatory BP control (intensive to achieve a goal 24-hour systolic BP of ≤ 130 mmHg or standard to achieve a goal 24-hour systolic BP of ≤ 145 mmHg) for a total of 36 months. Similar antihypertensive regimens will be used in both of the treatment groups with a general strategy of a renin-angiotensin blocking agent (ACE inhibitor or angiotensin blocker if ACE inhibitor not tolerated) along or in combination with a dihydropyridine calcium channel blocker and thiazide diuretics. Titration of antihypertensive therapies will be performed at monthly intervals for the first 3 to 6 months post-randomization to achieve goal systolic BP. The primary and secondary outcomes will be evaluated at baseline, and following 18 months and 36 months of therapy. Adverse events, tolerability, and health-related quality of life will be evaluated as well. Study patients will be seen on an an ad hoc basis throughout the trial for any/all issues associated with blood pressure, the administered antihypertensive therapies, and adverse events.

Sample Size and Population

It is estimated that 400 potential patients will be screened with MRI of the brain to detect the presence or absence of WMH and hypertension. There will be 200 subjects with demonstrable tWMH (> 0.5% of intracranial volume) randomized into 2 groups of 100 subjects with standard (24-h systolic BP<145 mmHg) or intensive (24-h systolic BP ≤130 mmHg) antihypertensive therapy strategies. No stratification is planned.

1. STUDY OBJECTIVES

1.1 Primary Objective

The primary objective of the study is to assess causality between 24-h systolic BP levels and preservation of mobility, cognitive and urinary function associated with lesser accrual of WMH in people over the age of 75 years. A key hypothesis of the trial is that intensive treatment of 24-hour systolic BP to levels of 130 mmHg or less will result in improved gait time, stair descent time, and maximal gait velocity compared to treatment of systolic BP to levels of 145 mmHg or less. This separation of ABP goals should achieve at least a ≥10 mmHg differences between groups. This difference has been shown to be responsible for the mobility decrements associated with WMH in older patients with systolic hypertension in our prospective cohort study.

1.2 Secondary Objectives

There are multiple secondary objectives of the trial:

- To determine whether accrual in WMH over 36 months mediates changes from baseline in mobility parameters.
- To evaluate the changes from baseline in cognitive function parameters in patients undergoing intensive treatment of 24-hour systolic BP (≤ 130 mmHg) versus those with standard treatment of 24-hour systolic BP (≤ 145 mmHg).
- To determine whether accrual in WMH over 36 months mediates changes from baseline in cognitive function.
- To evaluate the changes from baseline in urinary function parameters in patients undergoing intensive treatment of 24-hour systolic BP (≤ 130 mmHg) versus those with standard treatment of 24-hour systolic BP (≤ 145 mmHg).

- To determine whether accrual in WMH over 36 months mediates changes from baseline in urinary function
- To assess whether markers of tissue damage associated with microvascular disease of the brain (via diffusion tensor imaging) are linked to the functional measures (mobility, cognitive tests, and urinary function) at baseline and in the 2 treatment groups of blood pressure levels.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

White matter hyperintensities (WMHs), present in the magnetic resonance images (MRIs) of older people have been linked to hypertension and other vascular disease risk factors[1]. Evidence suggests that WMHs occur as a result of arteriosclerotic changes within the arteriolar wall and have been viewed as the manifestations of microvascular disease[2]. Large arterial and microvascular disease of the cerebral circulation share risk factors, (e.g., hypertension, diabetes) and may co-exist in an individual[1 3] although given the differences noted in Table 1 below, it is unclear that they both produce tissue damage through similar mechanisms[2 4].

Table 1. ***Comparison of the characteristics of stroke and microvascular disease***

Characteristic	**Stroke (large artery)**	**Microvascular disease**
Onset/progression	sudden/brief if any	ill-defined/gradual over years
Manifestations	focal neurologic deficit	functional limitations
Location	vascular distribution	grow from head/tail-lateral ventricles
Size	stroke(cm)→lacune (mm)	<1 mm
Vessel	large to small artery	Arteriolar

Pathophysiology	ischemic	Unclear

An increasing literature has associated WMHs to functional deterioration of mobility[5] [6] urinary control[7] and cognition[8]. The presence of WMH within brain pathways known to support mobility, cognition or voiding[9] [10] confirms the association between the functions and some of the proposed pathways. Detail seen on FLAIR and T2-weighted sequences of MRIs has allowed localization and quantification of the disseminated WMHs. Cross-sectional and prospective cohort studies have documented the relationships among WMH and neurologic function in older people and the distinctive nature of the distribution and volume of brain WMHs that are responsible for deterioration of these functions, particularly in the oldest groups.

2.2 Study Rationale

The BP in the clinic has been linked to brain WMH although predictors of quantitative WMH progression and their effect on the function of older persons are poorly understood. In our past work in this area, we evaluated the progression of WMH over 2-years in a cohort of 95 patients 75-90 years (mean baseline age, 82 years) who had office and ABP and volumetric MRI[11] Regression analyses were performed to assess the relations among changes in systolic BP, WMH, mobility and cognitive function. After 2 years, neither clinic BP nor change in clinic BP predicted progression of WMH whereas the 24-hour ambulatory BP and changes in ambulatory BP at 2 years significantly correlated with both WMH volume ($p<0.04$) and change in WMH ($p<0.003$). To determine the thresholds of 24-hour ambulatory systolic BP that correlated with decline in function and progression of WMH, analyses of tertiles of 24-hour BP were conducted. This analysis demonstrated an association for WMH and mobility indexes with level of systolic BP. In the high (144

mmHg) ambulatory BP groups, WMH was increased and mobility slower compared to the middle tertile (ambulatory systolic BP = 130 mmHg). Cut-point ranges for 24-h systolic BP at 2 years that separated WMH volume, declines in mobility and measures of cognitive function were developed. These data demonstrated that older subjects with 2-year 24-h systolic BP ≥140mmHg had significantly greater WMH, slower gait/stair descent times and a trend towards poorer executive function/processing speed than those with 24-h systolic BP <130mmHg. Gait speed in the high BP group decreased 0.15m/sec more than that in the low BP group and while this difference appears small, it represents between group change after only 2-years. Mobility impairment linked to WMH occurs gradually so that this decrement may be part of a long-term process which compromises gait velocity over 10 or more years. Hence, our results demonstrated that ambulatory BP, not clinic BP predicts the progression of WMH volume in older people within 2 years and is associated with significant differences in mobility. <u>These data suggest that an intervention using mean 24-hour systolic BP as the target could reduce progression of microvascular disease in the elderly and thus favorably impact function.</u>

Data from Hypertension in the Very Elderly Trial (HYVET) demonstrate antihypertensive therapy decreases stroke mortality even in patients in their mid-80s[12]. In HYVET, the goal of therapy was to reduce systolic BP to < 150 mmHg and this did result in a 39% reduction in stroke mortality linked to a 15 mmHg difference in systolic BP between active and placebo groups. To our knowledge, there is no other information on level of systolic BP and outcomes in a hypertensive population over the age of 80 years. Thus, the standard of care systolic BP is approximately 145-150 mmHg. Further, no clinical trial in hypertensive patients has used ambulatory BP to guide therapy and to assess cerebrovascular outcomes. Our study

has been designed to evaluate the functional impact of a clinically relevant separation in ambulatory systolic BP in an older population (that is, <130 mmHg versus <145 mmHg).

2.3 Hearing Sub-Study

Hearing Sub-Study Introduction and Specific Aims:

Small-vessel disease of the brain may cause white matter hyperintensities (WMHs) that are associated with the sequelae of uncontrolled hypertension and cardiovascular disease (Vermeer SE, Den Heijer 2003). The total burden of WMHs and WMHs at specific loci of the brain are correlated with low mobility in the elderly and reduce speed of cognitive functioning (Moscufo et al., 2011; Kaplan et al, 2009). Doctors White, Wolfson and colleagues at our institution show that WMHs are associated with increased ambulatory systolic blood pressure and reduced measures of executive function and cognitive processing (White et al., 2011). These data suggest that systolic blood pressure control may be a possible target for the reduction of microvascular disease in the brain and the functional sequelae of WMHs. A prospective study, Intensive versus Standard Ambulatory Blood Pressure Lowering to Prevent Functional Decline in the Elderly (INFINITY) at UConn Health is ongoing to study the link between WMHs, systolic blood pressure control, and neurological function.

The human brain coverts electrical impulses from the auditory nerve fibers and transforms them into meaningful auditory percepts and sensations (Willot, 1996). An individual's ability to hear would not be possible without an appropriately functioning central auditory nervous system. The central auditory nervous system is comprised of the auditory brainstem and the auditory cortex. The primary auditory cortex is located within the superior temporal gyrus of the temporal lobe and is composed of specialized

neurons that contribute significantly to hearing in noise performance (Musiek and Baran, 2007). Therefore, WMHs at specific loci of the brain, such as the primary auditory cortex, and lesions at these locations may contribute to decreased hearing in noise performance and some forms of age related hearing loss, known as presbycusis.

Presbycusis is described as sensorineural hearing loss that is associated with aging. Presbycusis is characterized by mild-to-moderate hearing loss in the high-frequency range with decreased speech understanding in background noise. Patients typically have slowed central processing of sounds and reduced ability to localize sounds. Presbycusis is present in approximately 50% of patients over the age of 70 (Fransen et al., 2003).

Schuknecht et al., categorized presbycusis based on findings from human temporal bone specimens (Schuknecht et al., 1964). He described 5 categories. 1) Sensory presbycusis was characterized by an abrupt change in the audiometric pattern is caused by the degeneration of hair cells. 2) Neural presbycusis was associated with a downward sloping pattern on the audiogram on pure-tone average testing and loss of cochlear nerve cells and central neural pathways. 3) Metabolic presbycusis was associated with atrophy of the stria vascularis and a flat hearing curve on audiometric testing. 4) Cochlear presbycusis was illustrated by a gradual sloping pattern on the audiogram with no histological changes in organ of Corti and neural structures. 5) Mixed presbycusis was a combination of the other types of presbycusis. To date, WMHs have not been studied as a cause or a contributing factor to hearing loss such as presbycusis. We propose to study the relative contribution of WMHs to presbycusis and hearing loss.

Hypothesis: WMHs at specific loci of the brain are critical to hearing, such as the primary auditory cortex, and lesions at these locations may contribute to some forms of presbycusis. A second hypothesis is that the global burden of WMHs may be associated with hearing loss, possibly as a marker of vascular changes in the cochlea.

Specific Aim 1: Are WMHs at specific loci of the brain along the auditory ascending pathways associated with presbycusis?

Expected outcomes and implications

We expect to find anatomical correlates of WMHs at specific loci of the brain on MRI diffusion tensor imaging that correspond to poor performance on audiometric testing, particular for hearing in noise performance. Brain imaging analysis will be blinded to audiometric analysis. The relative contribution of different brain loci to hearing loss will be compared.

Specific Aim 2: Is the global burden of WMHs in the brain associated with presbycusis? It remains a possibility that the global burden of white matter changes of the brain may be associated with presbycusis. Friedland et al., demonstrate, through a retrospective analysis that low-frequency hearing loss is associated with underlying cardiovascular disease, stroke and intracranial vascular pathology (Friedland et al., 2009). These authors hypothesize that this because vascular disease differentially impacts the apex of the cochlea, the area of the cochlea responsible for low frequency hearing. For this reason, we plan to study whether there is a correlation between WMHs in the brain associated with metabolic presbycusis, described by Schuknecht in histological specimens, that was associated with atrophy of the stria vascularis and a flat hearing curve on audiometric testing (Schuknecht et al., 1964). Such a correlation would allow

simple audiometric testing to be predictive of the presence of WMHs in the brain and the subsequent neurological sequelae.

Expected outcomes and implications

We expect to find a correlation of global burden WMHs to some forms of presbycusis. The pattern of hearing loss may be predictive of WHMs, which may have prognostic value for cardiovascular and neurological health.

Overall, a long-term goal of this sub-study is to understand the connection between WMHs in the brain, hearing loss, and possibly the connection between blood pressure control and hearing loss. The patient cohort in the INFINITY trial presents a unique population to study these questions.

Hearing Sub-study Methods

Many of the participants may have already undergone audiometric testing in some capacity through UConn Health. We will perform a retrospective analysis, specifically looking for audiometric testing in the past of patients who have completed the study (and the MRI) over one year ago.

Participants who have completed the main study over one year ago will undergo a retrospective chart review of only their hearing test records at UConn (Group 1). These records will be compared to the results of MRI scans and patient demographics as part of the main study. Only audiometric data will be collected as part of this retrospective review. Consent will not be obtained for this aspect of the study; a waiver of consent and HIPAA is submitted. These participants are all at least 78 and are no longer patients in the main study. Transportation may be difficult for many of them, some may have

moved, and some may have passed away. The waivers are necessary to avoid having these elderly participants who have completed the study over a year ago to return to UConn in order to only give permission to access hearing test records at UConn. Patients will not be contacted with the results of the retrospective study as they will not benefit from any further contact. Each patient would have already been counseled appropriately regarding medical management and possible rehabilitation strategies if hearing loss was demonstrated by a previous hearing test at UConn.

Participants who have completed the study/had an MRI in the past year will be contacted by mail with a letter explaining this sub-study and a phone number to call into if they are interested in participating (Group 2). Completed participants in Group 2 will only be contacted if they agreed to be contacted for future studies on the original study's HIPAA sign off. Participants will receive a letter describing the study (see attached letter). If participants in Group 2 are interested in participating they will call in to learn more about the study and schedule a visit to consent and undergo hearing tests.
Participants who are still active in the study will be given information (such as the ICF) about the hearing sub-study at their follow-up visits (Group 3). If interested in participating these participants will be consented at the main study follow-up or they schedule a consent visit and hearing test.

Consent will be performed by Dr. Roberts, Dr. White and approved study staff. All proposed audiometric testing will be performed by a licensed audiologist and are standard clinical metrics for hearing loss. Audiometric testing will include pure-tone audiometry, speech reception threshold testing, otoacoustic emmisions, and word recognition testing, AzBio sentence testing and ABR testing in some cases.

Data will be collected with standard forms used at the University of Connecticut in the clinical setting, to measure audiometric performance (AzBio Sentence Test List 1, UConn Health Audiometric Scoring sheet, dichotic digits score) and levels of tinnitus (Tinnitus Handicap Inventory) (see attached data collections forms).

All audiometric testing are standard clinical metrics for hearing loss and are routinely used in the clinical setting at the University of Connecticut. Audiometric testing will include a comprehensive audiogram consisting of pure-tone audiometry, speech reception threshold testing, otoacoustic emmisions, and word recognition testing. Subjects will also undergo AzBio sentence testing to investigate speech in noise performance. Pure-tone audiometry involves the presentation of soft tone stimuli, which requires a subject to indicate when a tone is heard. Speech reception/recognition testing requires the subject to repeat words presented at a decibel level adjusted for their hearing. Pure-tone audiometry and speech reception/word recognition testing takes place in an audiology sound booth and presented via headphones. Otoacoustic emissions are obtained by placing a soft probe in the ear canal and presenting soft tonal stimuli. The same probe will measure a response emitted back from the inner ear. Subjects will also undergo AzBio sentence testing to investigate speech in noise performance. AzBio sentence testing involves the subject repeating sentences at a volume adjusted for their hearing in the presence of background noise. This first hearing test session will take approximately 1 hour to complete.

For patients who demonstrate abnormalities on audiometric testing and have findings on imaging that may be accounted for audiometric findings, dichotic digit testing (DDT) will be performed. The DDT is a widely used test to screen for central auditory dysfunction. 25 sets of double-digit pairs (ie one, five) are presented for a total of 50 digits per ear.

The participant reports all digits heard for each presentation and a percent-correct score is calculated for each ear. Testing takes place in an audiology sound booth and will take approximately 1 hour.

If hearing loss is demonstrated or referral to a physician is indicated based on testing, participants will be offered a medical evaluation and will be treated accordingly. If a physician referral's indicated by audiometric testing is needed, the participant or participants insurance will be billed. A referral will only be given if the participant agrees to the referral. The participant will sign a release of information form allowing results of the hearing tests to be released to the participant or to the doctor.

Audiometric data will be compared to correlates assessed on morphological (T1, T2, and FLAIR) MRI, as well as on diffusion tensor MRI (DT-MRI). Patient demographics and clinical data that have already been collected through the INFINITY trial will also be compared.

Hearing Sub-study Risks and minimizations

A hearing test is safe with essentially no risks. At times, cerumen (ear wax) prevents the ability of an audiologist to perform a test. Should cerumen be present preventing testing, your ears will be cleaned by a physician prior to the hearing test. Confidentiality of the participant and the data collected is not guaranteed. To minimize this risk, data collection forms (see attached) will be coded and stored in a locked cabinet in a locked room. Only study staff will have access to this data.

3. GENERAL STUDY DESIGN

The study is a prospective, randomized, parallel group, open-label trial with blinded endpoints (PROBE), in older patients who have untreated 24-h systolic BPs between 150 and 180 mmHg mmHg) and evidence of at least 0.5% WMH volume on MRI. The key primary and secondary outcomes in the trial are change from baseline in mobility parameters (self-paced walk and stance times) and cognitive function (executive function, processing speed) with accrual of WMH providing the mediating mechanism for the functional decline. After baseline evaluation, patients will be randomized to the intensive group (goal 24-hour systolic BP ≤ 130 mmHg) or to the standard group (goal 24-hour systolic BP ≤ 145 mmHg) Assessments for the outcomes will be made at baseline and at 18 and 36 months post-randomization. Adverse events, tolerability, and health-related quality of life will be evaluated outcomes as well. We will perform complete assessments at times zero (baseline) and after 18 and 36 months (see Study Design Figure)

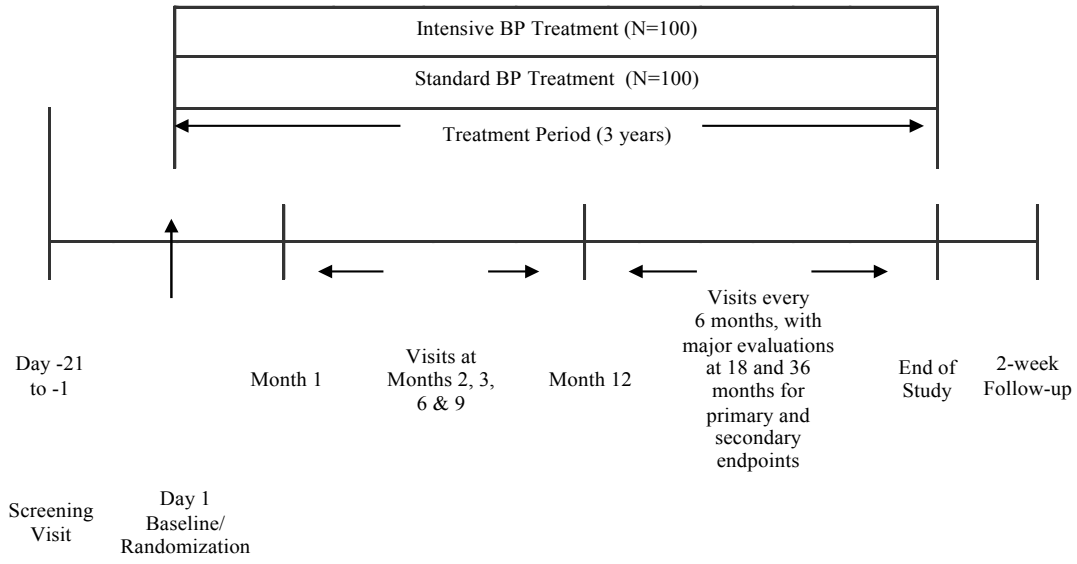


Figure. Design of Trial – Intensive BP Treatment – goal 24-hour ambulatory systolic BP ≤ 130 mmHg ; Standard BP Treatment – goal 24-hour systolic BP ≤ 145 mmHg

4. STUDY POPULATION

Three hundred men and women over the age of 75 years will be recruited and screened for the presence of systolic hypertension and WMH volume of ≥ 0.5% on MRI. It is expected that 2 of 3 patients in this age group will have WMH. Of the screened patients, 200 will be randomized in a 1:1 ratio to either the intensive or standard treatment arms. Every attempt will be made to have a substantial representation of minorities who have hypertension. It is estimated that 15% of the study population will be African-American and 10% will have Hispanic/Latino ethnicity. The inclusion and exclusion criteria for study entry are as follows:

4.1 Inclusion Criteria

To be included in the study, the following criteria must be met:

A. 75 years of age or older

B. Seated clinic systolic BP >150 mmHg in the untreated state

C. At risk for cerebrovascular disease (history of smoking, dyslipidemia, type 2 diabetes, longstanding hypertension, family history). Patients must have visible (0.5% WMH or more) white- matter hyperintensity lesions on screening magnetic resonsance imaging.

D. To achieve success in maintaining a 24-hour systolic BP of <140-145 mmHg in the standard treatment group or a systolic BP <125-130 mmHg in the intensive treatment group, patients will be eligible for inclusion if (1) their clinic systolic BP is 150-170 mmHg, and they are taking 0 to 2 antihypertensives, (2) their systolic BP is > 170 mmHg and they are taking 0 to 1 antihypertensive.

4.2 Exclusion Criteria

All candidates meeting any of the following exclusion criteria at baseline will be excluded from study participation.

1) Uncontrolled diabetes mellitus (HBA1c >10%)
2) History of stroke, dementia or clinically impaired gait (Mini-mental status exam score (MMSE) <24, Short Physical Performance Battery for gait (SPPB) < 9,)
3) Body Mass Index > 45 kg/m^2 and/or arm circumference > 44 cm)
4) Poor kidney function (defined as estimated GFR <30 ml/minute)
5) Active liver disease or serum transaminases >3 times the upper limit of normal
6) Major cardiovascular event (e.g. myocardial infarction) or procedure (e.g. cardiac bypass surgery) in past 3 months; stroke with residual gait abnormality
7) Uncompensated congestive heart failure (NYHA class III or IV or documented ejection fraction <30%)
8) Chronic atrial fibrillation that disallows ambulatory BP monitoring to be successfully performed
9) Medical conditions that limit survival to < 3 years
10) Non-dermatologic cancer diagnosed within 2 years
11) Organ transplantation requiring anti-rejection drug therapy
12) Severe and unexplained weight loss (>15%) in past 6 months
13) Medical need to undergo recurrent phlebotomy or blood transfusions
14) Current participation in another investigational trial
15) Unable to obtain informed consent

16) Factors limiting adherence to the interventions
17) MRI contraindications (including MRI-incompatible implants, severe claustrophobia).
18) Known carotid or intracranial arterial occlusive disease.

4.3 Study Enrollment Procedures at University of Connecticut Health Center

Study recruitment and enrollment. The study is a single-site randomized clinical trial that will be performed at the University of Connecticut Clinical Research Unit. Patients will be recruited from a variety of sources as described below. Three hundred patients will be enrolled into the trial in order to randomize 200 patients and complete 140 patients at 3 years of randomized treatment. Based on our prior experience in studying patients in this age group with hypertension and mild mobility issues, we project a 3-year attrition rate of approximately 30%. Recruitment will be carried out by several mechanisms, Including: A) contacting former research participants from the Cardiology and Hypertension faculty practices, the Center on Aging, and Neurology who have agreed to be informed of future studies, B) publically posted advertisements in addition to advertisements on the internet, radio and newspapers, C) Recruitment presentations conducted at community health centers, faith-based organizations and senior centers in conjunction with BP community clinics.

Recruitment will be extended into the greater Hartford region to improve minority participation. Advertisements will state that we are seeking volunteers for a treatment study aimed at older patients with hypertension willing to join a study involving the evaluation and treatment of high blood pressure, mobility and cognitive function. The

ads will state that antihypertensive medication, clinical visits, brain imaging, and other testing will be provided at no cost.

Following voluntary assent, interested individuals will be screened by phone for inclusion/exclusion criteria. Those meeting initial screening criteria will be invited to a Consent/Evaluation Visit during which informed consent will be obtained, followed by a medical history, physical exam, and tests to determine eligibility. Those not meeting study criteria will be referred for medical care. Patients not able to read and understand the consent form will be excluded from the study.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

REGIMENS, ADMINISTRATION, AND DURATION. Similar types of antihypertensive regimens will be used in both the *intensive and standard* treatment groups. As noted above, the BP goal in the *intensive* group is a 24-hour systolic BP mean of ≤ 130 mmHg and in the *standard* treatment group a 24-hour systolic BP mean of <145 mmHg. The types of therapy chosen for this trial are highly evidenced based – recent results from the HYVET study, a 2 year trial in high-risk, hypertensive patients >80 years demonstrated that diuretic and ACE inhibitor treatment reduced the risk of stroke using 150 mmHg as the treatment goal. In addition to efficacy and tolerability, ease of dosing plays a role in treatment adherence. Consideration of these issues as well as the finding from the ACCOMPLISH and ASCOT trials that use of an ACE inhibitor with a calcium antagonist were superior to a diuretic and ACE inhibitor are central to the proposed algorithms.
At the baseline, post-screening visit, an urn randomization procedure[2, 13] will be used to assign subjects to treatment conditions described below. There will be no stratification.

TREATMENT STRATEGY FOR THE INTENSIVE THERAPY GROUP. Patients in the *intensive group* will receive a low dose dihyropyridine calcium antagonist (amlodipine, 5 mg daily)[14] and a low dose ACE inhibitor (lisinopril 10 mg daily) at the time of randomization. If there is a history of ACE inhibitor intolerance (e.g. angioedema or cough), an angiotensin receptor blocker (ARB) (e.g. losartan 50 mg daily) will be substituted. Intensive group subjects will be seen monthly for titration of the 2 agents (maximal doses: amlodipine 10 mg and/or lisinopril 40 mg once daily) until achieving a clinic systolic BP of <135 mmHg – at that time (average time, 3 months), we will verify the 24-hour mean systolic BP is ≤130 mmHg. If the systolic BP has not reached goal on maximally tolerated doses of a calcium antagonist and an ACEi or ARB, low dose diuretic will be added (e.g., hydrochlorothiazide/12.5 mg daily or furosemide/20mg daily). If the BP goal is not achieved with 3 drugs, addition of daily dosing of one of the following agents is allowed: 1) beta-adrenergic blocker (first choice in a patient with known coronary disease), 2) alpha-adrenergic blocker (first choice in men with benign prostatic hyperplasia), 3) aldosterone antagonist (first choice in patients with low serum potassium levels). A loop diuretic may be substituted for a thiazide in patients whose estimated GFR is <50 ml/minute.[15] In subjects who had not reached the ABP goal at 3 months and who have further drug titration, the ABP will be repeated at 6 months to confirm that the 24-hour systolic BP goal has been achieved.

TREATMENT STRATEGY FOR THE STANDARD CARE GROUP. This group's goal of an ABP <145 mmHg is based on evidence from antihypertensive treatment strategies in older patients from HYVET[12] [16][16][16] in which clinic systolic BP values of <150 mmHg were associated with clinical benefits. Of note, there is no evidence that clinic systolic BP values <150 mmHg reduce stroke events in patients over the age of 75 years. As the 24-

hour BP mean is typically 5 to 10 mmHg lower than the clinic BP due to the effects of sleep, the goal in this group was set at 145 mmHg.

Treatment in this group will start with the ACEi lisinopril (initial dose 10 mg daily and maximal dose of 40 mg once daily) (or ARB if there is a history of ACEi intolerance). Subjects will be seen monthly until achieving a clinic systolic BP <150 mmHg with subsequent confirmation that the 24-hour BP goal of <145 mmHg has been achieved. If systolic BP does not reach the goal on maximally tolerated doses of an ACEi or ARB, a dihydropyridine calcium antagonist (e.g., amlodipine 5 mg up to 10 mg qd) will be added. Similarly, if the 24-hour systolic BP goal of <145 mmHg isn't achieved with this regimen, a diuretic will be added (e.g. hydrochlorothiazide/12.5 mg daily or furosemide/20mg daily). Similarly to the intensive BP group algorithm, a loop diuretic may be substituted for a thiazide in patients with chronic kidney disease. Finally, if goal BP is not achieved on 3 drugs, daily dosing of: 1) beta-adrenergic blocker, 2) alpha-adrenergic blocker, 3) aldosterone antagonist may be added. As in the intensive group, subjects not reaching their 24-hour systolic BP goal at 3 months and who have drug titration will have an ABP monitor performed at 6 months to confirm that goal 24-hour systolic BP has been reached.

DOWN-TITRATION OF ANTIHYPERTENSIVE THERAPY. Since it is unknown if lowering 24-hour systolic BP to the more intensive goal of ≤130 mmHg is beneficial in this age group, a reduction in the dose or number of antihypertensive drugs is allowed for patients in both groups but is likely to be more common in the standard group. The criterion that permits down-titration of medications in the standard care group is a clinic systolic BP <140 mmHg at 2 successive clinic visits or systolic BP <135 mmHg at a single visit accompanied by a 24-hour systolic BP value of <140 mmHg. The goal of down-titration is

to produce a usual care group systolic BP of 140-145 mmHg thus producing at least a 10 mmHg difference in ABP levels between the intensive and standard care groups.

5.2 Handling of Study Interventions

All study medications will be ordered and stored in the University of Connecticut Health Center Research Pharmacy (director, Ruth Lacasse, Pharm.D.) Clinical supplies will be ordered in bulk for both economical and practical reasons. The Research Pharmacy will prepare and dispense the labeled (study name and patient name are identified on the medication bottles) study medications to the research nurse as needed for individual patients. Unused study products will be returned to the pharmacy for disposal.

Drug accountability records are kept on every case report form and all dispensed and returned medications are quantitated by pill counts and recorded (including date and time of dispensing to study patients) on this form.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

Any medication for the treatment of a comorbid condition is typically acceptable as long as it does not belong to an antihypertensive drug class. It will be recommended that drugs that are known to raise the blood pressure or interfere with antihypertensive drug effect be used judiciously (e.g. decongestants with sympathomimetic activity, or chronic high-dose nonsteroidal anti-inflammatory agents). Study physicians will monitor concomitant drug use carefully and at every visit. Patients will be asked to always contact the research nurse to report any new prescriptions by physicians outside of the study for review.

5.3.2 Required Interventions (discussed in Section 5.1)

5.3.3 Prohibited Interventions

See 5.3.1 – otherwise, there are no other prohibited interventions.

5.4 Adherence Assessment

We will provide a prevention-oriented approach for adherence to study visits and medication compliance. Physicians and coordinators will be instructed on adherence issues as part of pre-trial training. Adherence will be monitored by self-report of each of the prescribed BP control medications at each visit. Pill counts of antihypertensive medications will be performed. In our experience as well as in the HYVET[12] and ACCOMPLISH[17] Trials with similar therapies those proposed in this trial, adherence to the regimen and study retention should be in excess of 75%.

Compliance to study medications is defined as taking 80 to 120% of prescribed medications based on pill counts.

5.5 Schedule of Evaluations

Assessment during the randomized clinical trial of intensive versus standard ambulatory BP control

	Screen	Baseline		RANDOMIZATION	MONTH									Post Study
		I	II		1	2	3	6	12	18	24	30	36	
Med Hx-Phys Ex	X				X					X			X	
Med Washout (0 to 4 week period)		X	X											
ECG	X					PRN*	PRN	PRN	PRN	X	PRN	PRN	X	
CBC, Chemistries		X				PRN	PRN	X	X	X	X	PRN	X	
MRI	X									X			X	
Gait/Mobility			X							X			X	
Cognitive Tests			X							X			X	
Urinary Function		X								X			X	
Clinic BP,HR,BMI	X	X	X		X	X	X	X	X	X	X	X	X	X
Med Titration					X	X	PRN	X	PRN	PRN	PRN	PRN		
Adverse Events			X		X	X	X	X	X	X	X	X	X	X
ABPM (24hr)			X				X	X**		X			X	
HOME BP			X						X	X	X	X	X	

*PRN laboratory testing for safety checks only (electrolytes, and renal function tests); note: due to the age of patients, medical staff and PIs will be available at all times for impromptu visits; ** - if needed based on 3 month ABPM and/or changes in clinic BP

5.6 Description of Evaluations

Resting clinic BP: Taken on a semi-automated digital device (Suntech TM2420, Morrisville, NC) with an appropriate cuff. After sitting 5 min, BP will be taken twice, 2-3 minutes apart in the non-dominant arm and averaged. BP readings will be taken between 8 and 11 am, before taking antihypertensive medication.

24-hour ambulatory BP Monitoring (ABPM): conducted after antihypertensive washout and prior to initiation of investigative therapy using the Oscar II BP device (Suntech Medical Instruments, Morrisville, NC) which has been validated independently.[18] The device is a light, comfortable automated BP recorder. Eighty BP

readings will be programmed during the 24-h study. Monitors will measure BP and heart rate every 15 min from 6 am to 10 pm, and every 30 min from 10 pm to 6 am. [19, 20]. Follow-up ambulatory BP recordings will be made at 3 months to evaluate response to therapy and at 6 months if medications were adjusted at 3 months to ascertain if systolic BP goals were achieved. Data will be transferred to Accuwin software program (Suntech Medical Instruments, Morrisville, NC) for analysis. Components of the ABPM for analysis will include the 24-hour mean systolic and diastolic BP, the awake and sleep BPs, and the early morning BP (the difference between the 2 hour post-awakening BP – the 2 hour pre-awakening BP) as previously described.[20, 21].

A **baseline electrocardiogram (ECG):** a standard 12-lead ECG will be obtained at baseline, 18 months and end of study – these will be assessed by study physicians Marfatia and/or White.

Laboratory tests (safety): CBC, glucose, BUN, creatinine, liver enzymes and urinalysis, sodium and potassium. Abnormal results will require further testing or referral for treatment before (or in lieu of) study participation.

Laboratory tests (research): lipid profile (Total, HDL and LDL cholesterol, and triglycerides).

Mobility Measures: Performance will be assessed primarily by timing.

- walking-moving
- Gait Speed: Gait speed will be measured as participants walk at a comfortable pace over an 8-meter course with 1 meter for acceleration and deceleration.
- Stair Ascent/Descent: stair ascent and descent will be used as a measure of walking-moving. We have previously shown stair descent time to be predicted by WMH[22]. Ascent and descent of 4 steps at a comfortable pace will be timed separately.
- changing-maintaining body position (3 with body position changes and 4 requiring maintenance of position):

- Supine-to-sit will occur on a mat table toward the preferred side at normal pace (hand-use allowed).
- Sit-to-stand will be from the mat table adjusted to leg length. Five repetitions will be performed at maximal pace with arms folded across the chest.
- Functional reach is measured in a forward direction using a wall-mounted meter stick.
- Maintenance of 3 stance postures (side by side, semi-tandem, tandem) as described in the Short Physical Performance Battery will be timed to a maximum of 30 sec. Thereafter, single limb stance using the preferred limb will be timed to a maximum of 30 sec.

Neuropsychological test battery: Testing will be performed in a quiet room by a trained technician using standardized procedures.

- Hopkins Verbal Learning Test (HVLT-R)[23] - provides an assessment of verbal learning and memory (immediate recall, delayed recall, and delayed recognition). There are 3 learning trials, in which a 12 word list is read aloud and subjects repeat the words immediately. Delayed recall uses a 20-25 minute delay after which, subjects repeat the set of words; it is because of the delay that this test must be given first. There is also a yes/no recognition trial in which subjects hear a randomized list that includes 12 words from the original list and 12 new words, 6 of which come from semantic categories on the original list. Subjects must identify the 12 words from the original list.
- Stroop Color- Word test[23] - Stroop Color and Word tests how well an individual suppresses a habitual response in favor of an unusual one thus assessing complex processing speed. Slower Stroop performance correlates with WMH.
- Controlled Oral Word Association Test[23] - Controlled Oral Word Association Test is a test of word generation from letters. This type of word fluency is typically

impaired in patients with frontal lobe lesions but spared in early Alzheimer's disease.

- Trail making test[23] - Trail Making tests speed of visual search, attention, mental flexibility and motor function. Performance on Trail Making is sensitive to early stages of dementia.
- Symbol Digit Substitution Test[23] - Symbol Digit Substitution evaluates processing speed. Subjects are asked to write the numbers corresponding to symbols in a *Key* at the top of the page. The *Key* shows the correct pairing of the symbols and numbers. Subjects are given 90 seconds in which to complete as many pairings as possible.
- Digit Span Test[23] - Digit Span tests auditory attention, concentration and working memory. The 2 parts of Digit Span – Digits Forward and Digits Backward—are administered separately. Digit Span number sequences are 2-8 random digits. Testing begins with 2 numbers that are read aloud at one digit per second. Subjects are asked to repeat the number sequence either as presented or reversed.
- California Computerized Assessment Package[24] - Cal CAP consists of 3 reaction time (RT) tests, a simple RT, a choice RT, and a serial RT. Simple RT measures general motor slowing. Choice RT is a go-no go paradigm, which measures response inhibition and processing speed. Serial RT measures divided attention and processing speed.
- Geriatric Depression Scale[25] was developed as a basic screening measure for depression in older adults.

Incontinence Assessment: Urinary incontinence (UI) will be measured by validated assessments. A yes answer to the question, "During the last 3 months, have you leaked urine (even a small amount)?" will define participants as incontinent. The type of UI will be evaluated by the 31Q questionnaire which uses 3 items to classify UI: presence of

leakage, situation of leakage (inability to reach toilet, physical activity, neither) and main type of UI (urge UI, stress UI, both, neither)[26]. Urinary incontinence severity will be measured using the Urinary Incontinence Severity Index in which leakage is depicted as none, slight, moderate, severe based on frequency and amount.[27] A brief version of the Urogenital Distress Inventory (UDI) will be used to measure the bother linked to urinary tract symptoms and UI based on a 4-point scale.[28] The functional impact of UI will be evaluated using the IIQ-7 (e.g., social activities) with a 4 point scale.[29]

Telephone Memory Impairment Screen. Death and study attrition are associated with age-related diseases. Failure to account for this informative censoring may result in biased estimates of dementia risk and cognitive decline. Hence, we will collect data by telephone to assess the degree to which living participants who fail to appear for their final assessment differ from participants who complete the study. Specifically, we will use telephone administration of a validated mobility assessment[30] to estimate mobility outcomes through multiple imputation or joint modeling that would have been observed had the participants appeared for their clinical assessment. We will use baseline and 18 month mobility data along with the answers to the telephone mobility assessment at all 3 time points to impute or jointly model the expected mobility outcomes, enabling us to predict the mobility outcomes that would likely have been observed at 36 months in subjects unable to appear for this assessment. While 18 month data are used in secondary analyses for major hypotheses, here the 18 month data are needed to estimate progression rate and the rate in patients not appearing for their final clinical assessment and are therefore essential for imputing the 36 month mobility outcome.

MRI acquisition will be performed at the University of Connecticut Health Center on a 1.5 Tesla Siemens Avanto scanner using the following parameters. 3D T1-weighted Magnetization Prepared Rapid Gradient Echo (MPRAGE): 120 contiguous 1.3 millimeter (mm)-thick sagittal slices, repetition time (TR)/echo time (TE)=2700/5 milliseconds (ms),

inversion time (TI)=950 ms, matrix size=192x256, field of view=230x310 mm^2, in-plane resolution =1.21x1.21 mm^2; 3D-T2: 120 contiguous 1.3 mm-thick sagittal slices, TR/TE=4300/349 ms, matrix size=190x256, field of view=230x310 mm^2, in-plane resolution =1.21x1.21 mm^2), and 3D-Fluid Attenuated Inversion Recovery (FLAIR): 120 contiguous 1.3 mm-thick sagittal slices, TR/TE=6500/349 ms, TI=2200 ms, matrix size=190x256, field of view=230x310 mm^2, in-plane resolution =1.21x1.21 mm^2). Whole brain diffusion tensor imaging (DTI) will be performed utilizing syngo DTI parameters at a diffusion-weighting strength of b =1000 s/mm^2; TR/TE = 2800/88 ms; 12-directions, matrix size=128x128 and FOV of 230 mm.

White matter lesion segmentation: Image pre-processing includes correction of magnetic field signal in-homogeneities[31], and linear affine registration of FLAIR and T2 series to the MPRAGE series.[32] Brain classification into normal WM, and T2-hyperintense WMH will be done using semi-automated segmentation. The final segmentation map will be obtained after expert review. Total WMH volume in milliliters (mL) will be calculated by multiplying voxel volume (mm^3) by the number of WMH pixels and dividing by 1000. To account for head size variability, volumes will be normalized and expressed as fraction of intracranial cavity volume (ICC).

Assessment of brain structural integrity through diffusion tensor imaging (DTI): We will assess the integrity of brain WM microstructure using DTI.[33] DTI will obtain measures of diffuse tissue damage, i.e. fractional anisotropy (FA) and mean diffusivity (MD), to complement WMH burden as additional MRI outcomes. While the WMH characterizes a volume of localized tissue damage, DTI measures aspects of tissue quality not otherwise available. Together the measures provide a more complete assessment that captures disease progress at different stages. DTI measures will thus be used as outcome markers in the same way as WMH. Specifically we will investigate 1) whether microvascular disease causes damage in normal-appearing WM (NAWM) on conventional (T2-weighted) MRI; and 2) whether controlling BP slows accrual of tissue

damage in the form of both NAWM as well as in WMH. Using the subject's brain segmentation output [34] as mask, we will identify the NAWM areas and within them determine FA and MD. We will characterize the cross-sectional and longitudinal relationships of FA and MD with WMH at baseline and follow-up to determine: 1) presence and degree of association; 2) predictive value of FA and MD as early indicators of functional (cognitive and mobility) deterioration and/or WMH accrual; and 3) effect of anti-hypertensive intervention on these DTI markers. Using this approach we will focus on WMH areas to quantitatively assess 1) the degree of structural integrity within areas of WMH compared to NAWM and 2) the change of FA and MD over time, to determine effectiveness of treatments in halting or slowing progress of fiber-tract damage.

The investigators performing mobility testing, cognitive testing, voiding function studies, and volumetric MRI will be blinded to treatment assignment until the T_{36} data are finalized and data lock has occurred.

MRI Reproducibility Sub-study

Ten to fifteen subjects will be scanned by a different technician to exam the reproducibility of the imaging protocol. These subjects will be scanned two consecutive times on the same day followed by a short break, following the same sequencing protocol each time. Recruitment of these subjects will occur at the 18-month and 36-month follow-up visits. At the 18-month or 36-month visits, prior to the follow-up MRI, the study physician/consentor will invite subjects to participate in the sub-study and will review sub-study consent and HIPAA consented at that time.

5.6.1 Screening Evaluation

Consenting Procedure

Consent authorization will not be obtained prior to preliminary screening through telephone calls initiated by potential subjects or for those interested in completing a brief screening questionnaire in person at community presentations. Those deemed eligible will sign a consent form at their first study visit.

Patients will be given time in the interview room privately to read the study consent form. After approximately 15-20 minutes, the study nurse or physician will review each section of the consent form together, taking time to answer any questions that arise. After any questions have been answered the study nurse or physician will move to the next section of the document and repeat the process. After the last section has been reviewed the patient will be asked to review the research project in his/her own words. If the subject provides an accurate summary s/he will be asked if s/he would like more time to consider their decision to participate and whether s/he would like to sign and date the consent form. If the summary is not accurate the coordinator will go over the relevant sections again. It is estimated that the informed consent discussion will take 30 to 45 minutes.

Signed consent forms will be stored securely in a locked file, separate from case report forms. Should significant findings arise that might affect a patient's willingness to continue to participate, the PI will submit a request for modification to the Informed Consent Form to the IRB and then, after obtaining approval, re-consent the subjects at the next regularly scheduled visit. If the updated consent form has not yet been approved by the IRB at the time of the visit a verbal explanation of the information will be provided to the patient and documentation of the explanation will be noted in the research record.

If the investigator or IRB determine that patients need to be contacted immediately depending on the nature of the information and the level of risk it

presents to subjects, the PI will communicate the information to the patients in the study as soon as possible and will document the contact with the patients.

Screening Procedures

- Study overview and consent
- Medical history
- Physical exam
- Standardized Clinic BPs
- ECG

5.6.2 Enrollment, Baseline, and/or Randomization

A. Enrollment Period

Baseline visit 1

- Fasting laboratory studies*
- Review and discussion of medication tapering if needed (by physician)
- Brief exam and standardized blood pressures
- Medical history, including evaluation of concomitant medications, adverse events for baseline
- **Laboratory Tests**: includes complete blood count, serum creatinine and blood urea nitrogen, glucose, ALT, urinalysis, total cholesterol, LDL and HDL cholesterol and triglycerides (fasting)
- **Baseline MRI** – (Radiology) Note: if patient has no WMH on baseline MRI, they will be excluded from further participation in the trial. No medication tapering will occur prior to the results of this study.

Baseline visit 2– this visit will be the first assessment following taper of prior antihypertensive therapy for those patients demonstrating WMH on the screening MRI.

- Medical history (intercurrent illnesses, medication history, adverse events)
- Standardized clinic BPs*

If patient is off antihypertensive agents at baseline or has been discontinued for 2 weeks with a mean clinic SBP ≥ 150 mmHg, patient will proceed with various tests below. If SBP < 150 mmHg, patient will return in 1 week to re-evaluate clinic BPs.

- *Standardized clinic BP measurements will be taken using the validated Suntech Medical Instruments TM24/7 in the non-dominant arm, seated position in duplicate and 1 upon standing prior to dosing of morning BP medications.
- Ambulatory BP monitoring
- Home BP monitoring – self-monitoring with a portable digital device, obtaining BP readings twice-daily in duplicate (morning, evening) for seven days. Patients will receive training on proper use of the device and record readings on separate sheet. Blood pressure readings will be obtained in the seated position prior to any morning and/or evening antihypertensive medications.
- Mobility battery - Gait Speed, Stair ascent and descent, Supine-to-sit, Sit-to-stand, Functional reach, Stance time, Single leg stance
- Cognitive battery – HVLT, Trail Making Test, Digit Span Test (Forward and Backward), Digit Span, Stroop Color and Word Test, Symbol Digit Substitution, Controlled Oral Word Association Test, California Computerized Assessment Package (Cal CAP), Geriatric Depression Scale.
- Incontinence questionnaires - UI 31Q, Urinary Incontinence Severity Index, Urogenital Distress Inventory (UDI), IIQ-7
- Mini-mental status exam

At this point, if all inclusion and exclusion criteria have been met, patient will be randomized to either A) Intensive ABP reduction group or B) Standard ABP reduction group. Treatment initiation will be as outlined in Section 5.1.

5.6.3 Post-Randomization Follow-up Visits

Visit 1 (1 month post-randomization) – At visit 1, patients will be evaluated for their clinic BP responses to assigned therapies. Procedures previously defined above will be repeated at this visit:

- Medical history, concomitant medications, adverse events, medication compliance
- Standardized clinic BP measurements, body weight and height
- Antihypertensive medication titration as appropriate based on clinic systolic BP (goals are < 135 mmHg if assigned to the Intensive group and < 150 mmHg if assigned to the standard group)
- Dispense medications for next month

Visit 2 (2 months post-randomization) – Patients will return for evaluation of antihypertensive response to therapy according to randomized treatment group. Procedures previously defined above will be done at this visit:

- Medical history, concomitant medications, adverse events, medication compliance
- Standardized clinic BP measurements, body weight and height
- Antihypertensive medication titration or down-titration as appropriate (goals are < 135 mmHg if assigned to the Intensive group and < 150 mmHg if assigned to the standard group; if the standard BP group patient has a systolic BP < 135 mmHg, antihypertensive medications will be reduced by the study physician)
- Safety laboratory studies (potassium, creatinine, BUN) if clinically necessary
- Electrocardiogram if clinically necessary
- Dispense medications for next month

Visit 3 (3 months post-randomization) – Patients will return for evaluation of antihypertensive response to therapy according to randomized treatment group. Procedures previously defined above will be done at this visit:

- Medical history, concomitant medications, adverse events, medication compliance
- Standardized clinic BP measurements, body weight and height
- Antihypertensive medication titration or down-titration as appropriate (goals are < 135 mmHg if assigned to the Intensive group and < 150 mmHg if assigned to the standard group; if the standard BP group patient has a systolic BP < 135 mmHg, antihypertensive medications will be reduced by the study physician)
- Safety laboratory studies (potassium, creatinine, BUN) if clinically necessary
- Electrocardiogram if clinically necessary
- Ambulatory blood pressure monitoring if clinic systolic BP has been stable for visits 2 and 3 according to treatment assignment. If not, patients will return in 2-4 weeks for re-assessment of BP stability. Antihypertensive drug titration will be based on ambulatory BP from this point forward.
- Dispense medications for next 3 months

Visit 4 (6 months post-randomization) – Patients will return for evaluation of antihypertensive response to therapy according to randomized treatment group. Procedures previously defined above will be done at this visit:

- Medical history, concomitant medications, adverse events, medication compliance
- Standardized clinic BP measurements, body weight and height
- Antihypertensive medication titration or down-titration as appropriate – ad hoc ambulatory BP can be performed here to address therapeutic goals and if deemed medically necessary.
- Safety laboratory studies (potassium, creatinine, BUN) if clinically necessary

- Electrocardiogram if clinically necessary
- Dispense medications for next 6 months

Visit 5 (12 months post-randomization) – Patients will return for evaluation of antihypertensive response to therapy according to randomized treatment group. Procedures previously defined above will be done at this visit:

- Medical history, concomitant medications, adverse events, medication compliance
- Standardized clinic BP measurements, body weight and height
- Antihypertensive medication titration or down-titration as appropriate; ad hoc ambulatory BP can be performed here to address therapeutic goals and if deemed medically necessary.
- Laboratory studies (potassium, creatinine, BUN, glucose, ALT, cholesterol profile)
- Electrocardiogram if clinically necessary
- Home BP monitoring
- Dispense medications for next 6 months

Visit 6 (18 months post-randomization) – Patients will return for evaluation of antihypertensive response to therapy according to randomized treatment group and will have comprehensive testing for WMH, mobility, cognitive function as well as blood pressure control. Procedures previously defined above will be done at this visit:

- Medical history, concomitant medications, adverse events, medication compliance
- Standardized clinic BP measurements, body weight and height
- Antihypertensive medication titration or down-titration as appropriate; ambulatory BP will be performed to evaluate achievement of therapeutic goals according to randomized treatment strategy.
- Safety laboratory studies (potassium, creatinine, BUN) if clinically necessary

- Electrocardiogram
- MRI acquisition at UCONN neuroradiology
- Mobility Testing
- Cognitive Testing
- Questionnaires related to urinary function, QOL
- Home BP monitoring
- Dispense medications for next 6 months

Visit 7 (24 months post-randomization) – Patients will return for evaluation of antihypertensive response to therapy according to randomized treatment group. Procedures previously defined above will be done at this visit:

- Medical history, concomitant medications, adverse events, medication compliance
- Standardized clinic BP measurements, body weight and height
- Antihypertensive medication titration or down-titration as appropriate; ad hoc ambulatory BP can be performed here to address therapeutic goals and/or if deemed medically necessary.
- Safety laboratory studies (potassium, creatinine, BUN) if clinically necessary
- Electrocardiogram if clinically necessary
- Home BP monitoring
- Dispense medications for next 6 months

Visit 8 (30 months post-randomization) – Patients will return for evaluation of antihypertensive response to therapy according to randomized treatment group. Procedures previously defined above will be done at this visit:

- Medical history, concomitant medications, adverse events, medication compliance
- Standardized clinic BP measurements, body weight and height

- Antihypertensive medication titration or down-titration as appropriate, ad hoc ambulatory BP can be performed here to address therapeutic goals and/or if deemed medically necessary.
- Safety laboratory studies (potassium, creatinine, BUN) if clinically necessary
- Electrocardiogram if clinically necessary
- Home BP monitoring
- Dispense medications for next 6 months

5.6.4 Completion/Final Evaluation

Visit 9 (36 months post-randomization) - Patients will return for evaluation of antihypertensive response to therapy according to randomized treatment group and will have final research testing for WMH, mobility, cognitive function as well as blood pressure control. Procedures previously defined above will be done at this visit:

- Medical history, concomitant medications, adverse events, medication compliance
- Standardized clinic BP measurements, body weight and height
- Antihypertensive medication will be prescribed/continued according to clinical goals for long-term management. Clinical follow-up will be arranged with either primary care physician, one of the study physicians, or both, depending on wishes of study patient.
- Safety laboratory studies (potassium, creatinine, BUN) if clinically necessary
- Electrocardiogram
- Ambulatory blood pressure monitoring
- MRI acquired at UCONN neuroradiology
- Mobility Testing
- Cognitive Testing
- Questionnaires related to urinary function, QOL

- Home BP monitoring

Early termination patients who complete at least 18 months of randomized therapy will be considered completed study patients and all comprehensive tests will be completed that were designated for visit 9.

SAFETY ASSESSMENTS

5.7 Specification of Safety Parameters

There are no experimental antihypertensive drugs in the trial. All medications that will be used are quite mature and have been in clinical use for > 15 years. Due to the age of the study patients, a number of serious and non-serious adverse events are expected and will be tabulated according to treatment assignment. Should a study patient have symptoms suggestive of vertebrobasilar insufficiency, whether prior to enrollment or during follow-up, the patient will be evaluated by a neurologist. All discontinuations due to serious and non-serious adverse events will be tabulated according to treatment assignment as well. These include:

Serious Adverse Events

- Major adverse cardiovascular events: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, unstable angina with urgent revascularization.
- Cardiac arrhythmias not associated with ischemia
- Hospitalized congestive heart failure
- Falls and/or syncope associated with injury (e.g fractures)
- Non-cardiovascular death
- Venous thromboembolic events (pulmonary embolism, deep venous thrombosis)
- Aortic aneurysm rupture, surgery
- Peripheral arterial surgery
- Coronary and peripheral revascularization, elective
- Major life-threatening infections

Non-Serious Adverse Events

- Potential symptoms/signs of low systolic BP (recorded systolic BP < 90 mmHg, postural reduction in systolic BP > 20 mmHg, lightheadedness, near syncope, falls without injury)
- Non-serious or non-severe adverse events according to body system: allergic, hematologic, gastrointestinal, pulmonary, renal, etc.)

Safety laboratory parameters

The key safety laboratory studies in the trial will include: hematocrit, potassium, sodium, creatinine, blood urea nitrogen, glucose, and AST. Each laboratory parameter will be evaluated in context of the individual patient. In general, large changes (e.g. doubling of serum creatinine) will be evaluated immediately, whereas small changes (e.g. a 15% increase in serum creatinine from baseline) will be repeated in a convenient fashion for the patient. Potassium supplements will be prescribed as needed.

5.8 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Serious adverse events and deaths will be recorded and reported to the NIA and DSMB within 48 hours of occurrence (or when the clinical staff become aware of the occurrence). Full descriptions of the serious adverse event and deaths will be made as soon as complete dossiers on the clinical information can be accumulated. Source documents from hospitalizations will be obtained in every case unless patient does not consent to do this. All reference to the patient will be redacted (name, names of relatives, date of birth, etc).

Stopping rule. A decision to discontinue the study will be based primarily on serious adverse events (SAEs). In discussion with the DSMB as it relates to timing of any decision making, the study will be stopped if unexpected and possibly study-related SAEs occur in 20% or more of the study population, or if an imbalance of these SAEs occur in 15% or greater of those participating in either treatment arm. We anticipate that unexpected and

possibly study-related SAEs will be rare, because participants will be receiving well tolerated antihypertensive therapies with substantial clinical safety oversight by the PI and research staff. Research nurses and staff who assist in the conduct of the trial will detect SAEs. In addition to the immediate disclosure, complete reports of SAEs will be reviewed at monthly staff meetings with the PIs, research nurses and physicians.

The NIH/NIA Adverse Events Monitoring Form will be used to collect detailed information about all serious adverse events, how they were handled, and their potential relationship to study participation. The procedures for SAE reporting also include written documentation using clinical notes related to the adverse event and specific forms detailing the event with a sign-off by clinical hypertension research MDs. Communication of recommendations and decisions from all parties (DSMB members, investigators, IRB) will be made in a timely manner as noted above. All of these individuals will receive a copy of the expected Serious Adverse Events Monitoring Form within 10 business days or sooner (48 hours) in the case of deaths and study-related SAES, at which point a decision will be made whether to convene a meeting.

Reviews of SAE and other safety data will be made at 4 month intervals by the DSMB members. Each DSMB member will vote on whether the study should: 1) continue as planned without changes; 2) continue after a protocol amendment; or 3) stop the trial pending further investigation. If, after this meeting, the DSMB votes to stop recruitment or requests a protocol modification due to concerns with patient safety, the IRB and NIH project officer will be informed immediately.

Other adverse events, such as cardiovascular, neurologic or renal adverse events not requiring hospitalization, will also be reported within 48 hours to the PIs by the study nurse and/or project manager. A determination of how to proceed will be made based on

consultation with the physician investigators on the project, or the patient's own physician, provided a release of information has been obtained. These adverse events will also be recorded on an Adverse Events Monitoring Form, which is similar to the SAE form.

A database of all adverse events will be maintained by the project manager in conjunction with the study nurse coordinator. Once per month, in research team meetings, all adverse events will be reviewed that occurred over the prior month, as well as over the course of the trial. In addition, the local IRB maintains records of all adverse events. Deaths and study related serious adverse events are reviewed immediately, and data are sent to NIH per standard policy. Aggregate data on reports of adverse events are reviewed on at least an annual basis by the IRB for study continuation, and at 4 month intervals by the external DSMB and study investigators. Any temporary of permanent suspension of patient accrual will be reported to the NIH project officer.

5.9 Reporting Procedures

Serious and non-serious adverse events will be documented as noted above and reported on a regular basis to the project director, the PI, the IRB, and NIA as indicated. Every 4 months, reports of aggregate data will be submitted to the data safety committee members that contain baseline demographics, retention data, adverse events and laboratory data, and any other data that will help in the assessment of the clinical trial. Based on this report, each DSM committee member will recommend on whether the study should: 1) continue recruitment unchanged; 2) continue with a protocol amendment; 3) stop recruiting pending further investigation. If, after this meeting, any DSM committee member votes to stop recruitment or requests a protocol modification, the IRB will be informed.

5.10 Follow-up for Adverse Events

Participants who experience a significant medical problem requiring an overnight hospitalization at an acute care facility will be defined as having experienced a serious AE, which are expected to occur fairly regularly in this age group. Types of SAEs in the hypertensive population with vascular disease are as follows: cardiovascular complications of hypertension including myocardial infarction, stroke, arrhythmias, and heart failure. Other non-serious adverse events (AEs), such as shortness of breath, dizziness, or near syncope not requiring hospitalization, will also be reported. All SAEs and AEs result in the completion of an Adverse Events Monitoring Form within 2 days of discovery to the PI and/or study coordinator by the research nurses and/or research assistants.

The Adverse Events Monitoring Form is adapted from one being used in the NIH Clinical Trials Network and our other ongoing trials. This form collects detailed information about all adverse events, how they were handled, and their potential relationship to study participation. The procedures for adverse event reporting also include written documentation using clinical notes related to the adverse event and specific forms detailing the event with a sign-off by all appropriate supervisory personnel.

We anticipate that unexpected and possibly study-related SAEs will be rare, because participants will be receiving well-tolerated, FDA approved pharmacotherapy. None of the study procedures are associated with SAEs.

As noted above, clinical research staff will review all past month and study cumulative AEs and SAEs at monthly meetings. All research staff members have completed required institutional training on research with Human Subjects. Research staff are trained in adverse event reporting and understand that their responsibility is to document and report adverse events reported by study participants, independent of determinations made at the time or later of the relationship between the event and participation in the study.

Adverse events will be followed until they are resolved or considered stable by the clinical investigative team. We have an AE/SAE log in every case report form that will be updated as the disposition of the adverse event evolves. The categories include a) resolved, b) reduced, c) unchanged.

5.11 Safety Monitoring

This study has a formal data safety monitoring plan and will be evaluated by an independent Data Safety Monitoring Board (DSMB) (see appended draft DSMB Charter).

6. INTERVENTION DISCONTINUATION

A. Patients will be discontinued from their antihypertensive intervention if it is deemed that the treatment(s) or blood pressure level is no longer safe or appropriate based on clinical condition (e.g. development of congestive heart failure that mandates a specific regimen or development of a terminal malignancy).

B. Potential reasons for discontinuation of the intensive treatment might include untoward symptoms associated with low blood pressure related to development of a new morbidity (e.g. blood loss, sepsis) or intolerance to therapy (e.g. lightheadedness/syncope. In rare cases, hyperkalemia or hyponatremia may develop that would be unmanageable under the constraints of the protocol-drive therapies. Hypokalemia will be managed with aggressive potassium replacement to maintain serum levels > 3.5 meql/L.

C. As this is an intention-to-treat trial, patients who discontinue treatment interventions will be invited to participate in clinical follow-up and all comprehensive outcome studies at months 18 and 36 of the trial.

D. In the event of temporary discontinuation of antihypertensive treatment (e.g. need to withhold antihypertensive medications due to surgery, post-operative bleeding, infection or other causes of low blood pressure), reassessment of these individual patients will be made

in the research clinic for a return of BP levels towards baseline, and study medications will then be resumed.

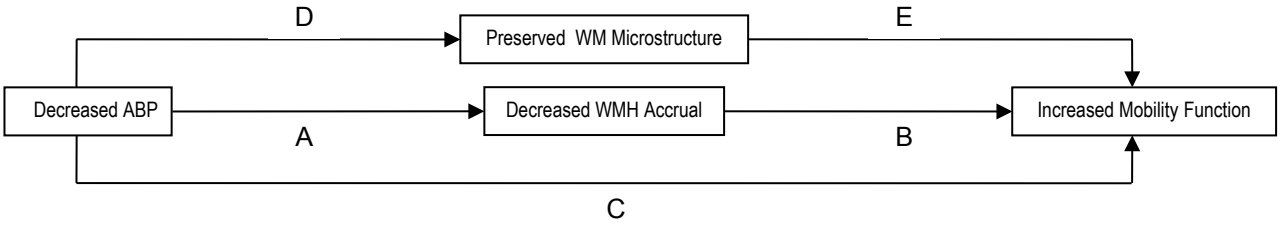
7. STATISTICAL CONSIDERATIONS

7.1 General Design Issues

General considerations: Predictor, covariate, and dependent variables will be examined for outliers and data beyond the range of human performance. We will analyze variables on the original measurement scale, or on a scale that allows meaningful interpretation e.g., when an inverse transformation on a time measure results in a speed interpretation. The primary analyses (hypotheses 1, 2 and 3) will be intention-to-treat.

Hypothesis models, analysis plan, and power estimates for primary outcomes were developed with PASS 2008[35] and SAS PROC POWER[36] were used for estimation of power.

8.2 Hypotheses and Statistical Analyses



The Figure shows graphically how our hypotheses relate to one another. Hypothesis 1 tests the combined effects of paths A, B, C, D & E i.e., the total effect of BP on mobility. Hypothesis 2 tests path A, Hypothesis 3 tests path D, Hypothesis 4 tests path B+E; together Hypotheses 2, 3 and 4 together test the effect of BP on mobility mediated through BP's effects on WMH and WM microstructure. Hypothesis 5 tests the relative importance of paths A and B to that of path C, i.e., the degree to which the effect of BP on mobility is explained by WMH. Hypothesis 6 tests the relative importance of paths D and E to that of path C, i.e., the degree to which the effect of BP on mobility is explained by changes in WM microstructure.

Hypothesis path diagram

Hypothesis 1: Intensively treating 24-h systolic BP to a goal of <130 mmHg versus standard BP control of <145 mmHg will lead to faster walking speeds at T_{36}. (Paths A&B+C+D&E)

Hypothesis 2: Intensively treating 24-h systolic BP to a goal of <130 mmHg versus standard BP control <145 mmHg will lead to smaller total WMH volume. (Path A)

Hypothesis 3: Intensively treating 24-h systolic BP to a goal of <130 mmHg versus standard BP control <145 mmHg will stabilize brain WM microstructural integrity (FA and MD) at T_{36}. (Path D) We will perform 3 sets of analyses for hypotheses 1, 2 & 3:

a. Multiple linear regression will be performed with treatment group (intensive vs. standard) as the predictor of interest. Gait velocity at T_{36} is the primary outcome for hypothesis 1, WMH at T_{36} is the primary outcome for hypothesis 2, and DTI indices (FA and MD) are the primary outcomes for hypothesis 3. The analysis will be intention-to-treat. Age, sex, and 24 hour SBP at T_0 (baseline) will be included as covariates, along with other demographic factors for which the treatment groups are not comparable. **The analysis for hypothesis 1 is the proposal's primary efficacy analysis and thus the proposal is powered to address this analysis (see Sample size estimation).**

b. We will repeat analyses 1a, 2a and 3a but with gait velocity at T_{18}, total WMH at T_{18}, and DTI indices at T_{18} as the primary outcomes. A comparison of these analyses with analyses 1a and 1b will determine the time course of the intervention's effects. In particular, it will be important to determine if these effects occur early (T_{18}) or require a 3-year treatment period. In addition, for participants who are present at T_{18} but not T_{36}, the data from T_{18} will be used to estimate the effect of informative loss to follow-up. (See Missing Data)

c. We will further examine the progression of mobility and WMH changes using a progression model using methods adapted from Diggle:[36]

$$Y_{i0} = b_{i0} + \beta_T (X_i) + \text{cross sectional covariates} + \text{residual error}$$
$$Y_{i18} = b_{i0} + \beta_T (X_i) + \beta_L + \beta_E (X_i) + \text{cross sectional covariates} + \text{longitudinal covariates} + \text{residual error}$$
$$Y_{i36} = b_{i0} + \beta_T (X_i) + \beta_L^* + \beta_E^* (X_i) + \text{cross sectional covariates} + \text{longitudinal covariates} + \text{residual error}$$

Here, $Y_{i0}, Y_{i18},$ and Y_{i36} are the outcomes (mobility or imaging) at T_0 T_{18} and T_{36} for study participant $i,$ and X_i is the treatment group assignment indicator for study participant $i,$ and b_{i0} is a random intercept used to account for the fact that repeated measurements on individuals are not independent; the other $\beta_j's$ are fixed effects in this example although we will consider the possibility that treating them as random effects will add to the model fit. The model will be fit as a linear mixed model.[37, 38] The parameters of interest are $\beta_E,$ and $\beta_E^*,$ the difference in the outcome progression rate (mobility or imaging) between the treatment groups at T_{18} and T_{36}. If the difference in the rate of progression is constant during follow-up, we would expect β_E^* to approximately equal $2 \times \beta_E$. This allows a more powerful and rigorous test of whether the intervention's effects are manifested quickly or over the long-term. Additional secondary analyses will use the T_{18} data to determine temporal continuity of the trends and as a partial assessment of the effect of dropout. Additional secondary analyses will use logistic regression with severity of urinary incontinence at T_{36} and T_{18} as an ordinal outcome.

Other mobility measures will also be examined as secondary outcomes in models otherwise identical to those in a, b, and c. The analyses will be repeated for cognition, with the speed obtained on Trailmaking B at T_{36} as the primary outcome and other cognitive measures as secondary outcomes. Additional secondary analyses will use logistic and ordinal models with the same predictors and incontinence presence and severity, respectively as outcomes; the progression model (c) will be fit as binary or ordinal generalized linear mixed models.

Hypothesis 4: Reduced total WMH and decreased markers of tissue damage on DTI at T_0 and at T_{36} are linked to better mobility at T_{36}. (Paths B+E) The same outcomes will be used for this hypothesis as in hypothesis 1, with identical analyses except that WMH, and DTI indices (FA and MD) as continuous variables will be the primary predictor of interest. The power for this hypothesis as expressed as increased in explained variability (R^2) will be the same as for hypothesis 1: 85% power to achieve an increase in R^2 of 0.0533; we actually observed an increase in R^2 of 0.1658, to 0.2925, as the effect of tWMH, corresponding to a reduction in gait

velocity of 0.0063 m./sec. for each 0.1% increase in tWMH. The analyses will be repeated for gait velocity at T_{18} with a model corresponding to analysis b, and for the following progression model replacing the model for analysis c:

$$Y_{i0} = b_{i0} + \beta_C (X_{i0}) + \text{cross sectional covariates} + \text{residual error}$$
$$Y_{i18} = b_{i0} + \beta_C (X_{i0}) + \beta_L (X_{i18} - X_{i0}) + \text{cross sectional covariates} + \text{longitudinal covariates} + \text{residual error}$$
$$Y_{i36} = b_{i0} + \beta_C (X_{i0}) + \beta_L (X_{i36} - X_{i0}) + \text{cross sectional covariates} + \text{longitudinal covariates} + \text{residual error}$$

Here, $Y_{i0}, Y_{i18}, \text{ and } Y_{i36}$ are the outcomes (mobility or imaging) at T_0, T_{18} and T_{36} for study participant i, $X_{i0}, X_{i18}, \text{ and } X_{i36}$ the tWMH at T_0 T_{18} and T_{36} for study participant i, and b_{i0} is a random intercept that is used to take into account the fact that repeated measurements on individuals are not independent. The model will be fit as a linear mixed model[37]. Again the other β_j's are fixed effects although we will consider the possibility that treating them as random effects will add to the model fit. The parameters of interest are β_C and β_L, the cross-sectional and longitudinal effects of the imaging measures on mobility over the 36-month follow-up. As secondary analyses we will consider interactions with treatment group and nonlinear effects in time. Analyses will be repeated for the other mobility and cognitive measures, also as linear mixed models, and urinary incontinence presence/severity as binary and ordinal generalized linear mixed models.

Hypothesis 5: **Total WMH at T_0 and at T_{36} mediate the effect of treatment group, showing that the mechanism by which reduced ABP is linked to better mobility occurs by reducing total WMH.**(Paths C - A&B) Mediation models allow the evaluation of hypotheses using biological mechanisms. In this case, we believe that much of the salutary effect of reduced ABP results from reduced WMH. Assessing mediation involves estimating direct effects (Path C, above) and indirect effects (Paths A and B, above) in multistage predictor models by adding potential mediators to models describing the effect of a predictor on the outcome. To the extent by which WMH mediates the effect of BP, the effect of BP will be reduced in the model that includes WMH compared to the model not including WMH. We saw this in our observational study, as the adjusted effect of SBP in the pseudo-treatment group was reduced

from a .15 m/sec. to a .1 m/sec. difference in gait velocity when WMH was added as a model predictor.

Product of coefficients methods[35,36] will be used for formal statistical inference regarding the mediation. Specifically, we will estimate the product of the effect estimated for hypothesis 2 corresponding to Path A (the effect of intervention group on total WMH at T_{36}), and the effect estimated for hypothesis 3 corresponding to Path B (the effect of WMH at T_{36} on gait velocity at T_{36}). The magnitude of this product turns out to be proportional to the change in the effect of intervention group on gait velocity at T_{36} when WMH at T_{36} is added to a regression model of gait velocity at T_{36} as a function of intervention group. Similar models will be used to assess outcomes at T_{18}, and the cognitive outcomes. As formal tests for mediation using the product of coefficients method require larger sample sizes than available in this study, we will treat results from analyses in Hypothesis 5 as preliminary, to be potentially verified by a larger study should the main effects in Hypotheses 1-3 be confirmed.

Hypothesis 6: Diffusion tensor imaging (DTI) indices (FA, MD) at T_0 and at T_{36} mediate the effect of treatment group, showing that the mechanism by which reduced ABP is linked to better mobility occurs by preserving brain WM microstructural integrity (FA, MD). (Paths C – D&E) The same analysis as used for hypothesis 5, except that the mediating effect of the DTI indices will be assessed.

Missing Data.

Death and study attrition are associated with age-related diseases. Failure to account for this informative censoring may result in biased estimates of dementia risk and cognitive decline.[37] Hence, we will collect data by telephone to assess the degree to which living participants who fail to appear for their final assessment differ from participants who complete the study. As mentioned above, we will use telephone administration of a validated mobility assessment[39] and the method developed by Dr. Hall and colleague[30] to estimate mobility outcomes through multiple imputation or joint modeling that would have been

observed had the participants appeared for their clinical assessment. While our primary efficacy outcome analysis will be limited to participants who complete the study, this will be the first trial in aging with the potential to assess the impact of informative dropout beyond usual sensitivity analyses.

8.3 Sample Size and Randomization

We conservatively estimate that at least 140 of the original 200 participants will complete assessments at 35 months. We analyzed a subset of participants in our earlier observational study in order to mimic the results of the two treatment groups we expect to see in the intervention study. for a standard care arm, we selected participants in the observational study who had 24 hour systolic BP between 140 and 150 mmHg, inclusive, at follow-up, and for the intensive treatment arm, we selected participants with 24 hour Systolic BP between 120 and 130 mmHg, inclusive, at follow-up. A regression of gait velocity over 8 feet on our covariates age, sex, and 24 hour systolic BP at baseline showed an r^2 of 0.1267. If we see similar results in the intervention study, 140 participants (70 in each group) will give us 85% power to observe an increase in r^2 of 0.0533 to 0.1800. In our prior observational study, we saw an increase in r^2 of 0.1082 to 0.2349, with a difference in gait speed between the two simulated treatment groups of 0.15m./sec. While the 0.15m/sec gait speed difference between the low and high BP groups appears small, it represents only 2 years of observation. Mobility impairment linked to WMH is a long-term decremental process that limits gait velocity over 10 or more years. Thus a “small” 2-year differential is both believable and meaningful. We are therefore confident that the proposed study has ample power to find smaller yet clinically significant effects for our primary outcome. A regression of total WMH on covariates age, sex, and 24 hour systolic BP at baseline showed an r^2 of 0.1162. Similar results in the intervention study imply 85% power to observe an increase in r^2 of 0.0540 for the effect of the treatment arm, to 0.1702. We actually observed an increase of 0.0861, to 0.2023, in the prior observational study, corresponding to a difference between the two simulated treatment groups of 0.93% total WMH.

8.3.1 Treatment Assignment Procedures

This trial is an open-label PROBE design – clinical staff and investigators will be aware of treatment assignment for safety and management. Those observers performing outcome tests (WMH calculations, mobility testing, cognitive assessment, and urinary function testing) will remain blinded to individual treatment group assignments until the end of the trial. .Interim analyses and Stopping Rules

8.3.2 Interim Analyses and Stopping Rules For Safety

No interim analysis is planned that would result in stopping the trial early.

Stopping rule for safety. A decision to discontinue the study will be based primarily on serious adverse events (SAEs). In discussion with the DSMB as it relates to timing of any decision making, the study will be stopped if unexpected and possibly study-related SAEs occur in 20% or more of the study population, or if an imbalance of these SAEs occur in 15% or greater of those participating in either treatment arm. We anticipate that unexpected and possibly study-related SAEs will be rare, because participants will be receiving well tolerated antihypertensive therapies with substantial clinical safety oversight by the PI and research staff. Research nurses and staff who assist in the conduct of the trial will detect SAEs. In addition to the immediate disclosure, complete reports of SAEs will be reviewed at monthly staff meetings with the PIs, research nurses and physicians.

7.4 Outcomes

See Section 8.2 for analysis of outcomes.

8. DATA COLLECTION AND QUALITY ASSURANCE

8.1 Data Collection Forms

Appended to the protocol are case report forms (CRF) that will be used for all other clinical

data. The patients name or other identifying information is never recorded on the CRF or recorded by those individuals involved in the outcome assessments. Rather a unique study code # is given to each patient without regard to randomization treatment group. Laboratory reports and informed consent forms that do identify the study patients are maintained with a key of unique study code # in a locked cabinet in the clinical research unit with a back up list in the PI's office.

8.2 Data Management

This is a single site study. Our data management procedures are mature and standardized. Data are entered from the CRFs and outcome assessment forms into ACCESS, which allows ranges to be defined a priori, minimizing data entry errors. Data will later be imported into SPSS, and within- and cross-file checks are used for cleaning and checking anomalous values. Data files are backed-up regularly to a secure server.

8.3 Quality Assurance

8.3.1 Training

We use centralized training, certification, and reliability testing for consistency across projects. In addition, monthly staff meetings will be held to review and remind staff on data collection, informed consent, adverse events, confidentiality, etc, to research staff to enhance fidelity.

8.3.2 Quality Control Committee

Not applicable.

8.3.3 Metrics

We have developed reproducibility methods for all outcome assessments. These methods allow us to develop a range of coefficients of variation for the various measures over time.

8.3.4 **Protocol Deviations**

The project manager of the study and project statistician will regularly be reviewing the individual case report forms for deviations from the protocol as data are entered into the ACCESS database. Protocol deviations will be minimized by effective communication among clinical staff and study participants. In all cases, the deviations will be documented in a separate study binder and those of important magnitude must be reported to the University of Connecticut Institutional Review Board for assessment.

8.3.5 **Monitoring**

As this is a single center study, external monitoring will not be in place. The institution does have a voluntary (and random involuntary) auditing process in place for all Human Subjects Trials that is conducted by an officer of the Office of Clinical and Translational Research. In theses audits, a random sample of CRFs are evaluated for protocol violations, as well as assessment of regulatory documents, informed consent forms and pharmacy records.

9. PARTICIPANT RIGHTS AND CONFIDENTIALITY

9.1 Institutional Review Board (IRB) Review

The study protocol and the informed consent document has been reviewed and approved by the IRB committee responsible for oversight of the study (University of Connecticut Health Center IRB). Any subsequent modifications will be reviewed and approved by the University of Connecticut Health Center IRB.

9.2 Informed Consent Forms (Appendix)

A signed informed consent form (ICF) will be obtained from each participant. The ICF will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant and this fact will be documented in the participant's record.

9.3 Participant Confidentiality

Any data, forms, reports, and other records that leave the site will be identified only by a participant identification number (Participant ID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using participant IDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIA, and the OHRP.

9.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIA, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

10. COMMITTEES (NOT APPLICABLE OTHER THAN DSMB – SINGLE CENTER STUDY)

11. PUBLICATION OF RESEARCH FINDINGS

Publication of research findings are under the direction of the Principal Investigators and other Key Personnel.

12. REFERENCES

1. Vermeer SE DHT, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Incidence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. *Stroke.* Feb 2003;34(2):392-396.
2. Wolfson L. Microalbuminurea as an index of brain microvascular dysfunction. *J Neurol Sci.* Sep 15 2008;272(1-2):34-35.
3. Kuller LH LW, Jr., Arnold AM, Bernick C, Bryan RN, Beauchamp NJ, Jr. White matter hyperintensity on cranial magnetic resonance imaging: a predictor of stroke. *Stroke.* Aug 2004;35(8):1821-1825.
4. Rosenberg G. Matrix metalloproteinases and their multiple roles in neurodegenerative diseases. *Lancet Neurol.* Feb 2009;8(2):205-216.
5. Benson R GC, Wei X, et al. Older people with impaired mobility have specific loci of perventricular abnormality on MRI. . *Neurology.* 2002;58:48-55.

6. Baloh RW YQ, Socotch TM, Jacobson KM. White matter lesions and disequilibrium in older people. I. Case- control comparison. *Arch Neurol.* 1995;52(10):970-974.
7. Sakakibara R HT, Uchiyama T, Yamanishi T. Urinary function in elderly people with and without leukoaraiosis: relation to cognitive and gait function. . *J Neurol Neurosurg Psychiatry.* Nov 1999;67(5):658-660.
8. Junque C PJ, Vendrell P, et al. Leuko-araiosis on magnetic resonance imaging and speed of mental processing. . *Arch Neurol.* 1990;47(2):151-156.
9. Kuchel GA MN, Guttmann CR, et al. Localization of brain white matter hyperintensities and urinary incontinence in community-dwelling older adults. *J Gerontol A Biol Sci Med Sci.* Aug 2009;64(8):902-909.
10. Kaplan RF CR, Moscufo N, et al. Demographic and biological influences on cognitive reserve. . *J Clin Exp Neuropsychol.* Mar 31 2009:1-9.
11. White WB WL, Wakefield DB, Hall CB, Campbell P, Moscufo N, Schmidt J, Kaplan RF, Pearlson GP, Guttmann CR. Average Daily Blood Pressure, not Office Blood Pressure, Predicts Progression of Cerebrovascular Disease and Functional Decline in Older People. *Circulation.* 2011 (revised manuscript submitted).
12. Beckett NS PR, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. . *N Engl J Med.* May 1 2008;358(18):1887-1898.
13. Schulz KF GD. Generation of allocation sequences in randomised trials: chance, not choice. *Lancet.* Feb 9 2002;359(9305):515-519.
14. Group A. Effects of intensive blood pressure control in type 2 diabetes. *New Engl J Med.* 2010;362(17):1575-1585.
15. Brater D. Diuretic therapy. *N Engl J Med.* Aug 6 1998;339(6):387-395.
16. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med.* May 1 2008;358(18):1887-1898.
17. Jamerson K WM, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med.* Dec 4 2008;359(23):2417-2428.
18. Cameron JD SI, Reed E, McGrath BP, Dart AM, Kingwell BA. Accuracy of automated auscultatory blood pressure measurement during supine exercise and treadmill stress electrocardiogram-testing. . *Blood Press Monit.* Oct 2004;9(5):269-275.
19. White W. Expanding the use of ambulatory blood pressure monitoring for the diagnosis and management of patients with hypertension. *Hypertension.* Jan 2006;47(1):14-15.
20. White WB WC, Borer JS, et al. Risk of cardiovascular events in patients receiving celecoxib: a meta-analysis of randomized clinical trials. . *Am J Cardiol.* Jan 1 2007;99(1):91-98.
21. Campbell P GN WD, Wolfson L, White WB. Long-term reproducibility of ambulatory blood pressure is superior to office pressure in the very elderly. *J Hum Hypertens.* 2010;24:749-754.
22. Wakefield DB MN, Guttmann CR, et al. White Matter Hyperintensities Predict Functional Decline in Voiding, Mobility and Cognition in Older Adults. *J Am Geriatr Soc.* 2010;58:275-281.
23. Strauss E SM, Strauss. . *A compendium of neuropsychological tests*. New York: Oxford; 2006.
24. Miller EN SP, Visscher B. Computerized and conventional neuropsychological assessment of HIV-1- infected homosexual men [see comments]. *Neurology.* 1991;41(10):1608-1616.
25. Yesavage JA BT, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. . *J Psychiatr Res.* 1982;17(1):37-49.
26. Brown JS BC, Subak LL, et al. The sensitivity and specificity of a simple test to distinguish between urge and stress urinary incontinence. . *Ann Intern Med.* May 16 2006;144(10):715-726.
27. Hanley J CA, Hagen S. Validity study of the severity index, a simple measure of urinary incontinence in women. . *BMJ.* May 5 2001;322(7294).
28. Uebersax JS WJ, Shumaker SA, McClish DK, Fantl JA. Short forms to assess life quality and symptom distress for urinary incontinence in women: the Incontinence Impact Questionnaire and the Urogenital Distress Inventory. Continence Program for Women Research Group. *Neurourol Urodyn.* 1995;14(2):131-139.

29. Harvey MA KB, Griffith D, Versi E. The Incontinence Impact Questionnaire and the Urogenital Distress Inventory: a revisit of their validity in women without a urodynamic diagnosis. . *Am J Obstet Gynecol.* jUL 2001;185(1):25-31.
30. Verghese J, Katz MJ, Derby CA, Kuslansky G, Hall CB, Lipton RB. Reliability and validity of a telephone-based mobility assessment questionnaire. Age Ageing 2004; 33: 628-632.
31. Sled JG ZA, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. . *IEEE Trans Med Imaging.* Feb 1998;17(1):87-97.
32. Jenkinson M SS. A global optimisation method for robust affine registration of brain images. . *Med Image Anal.* Jum 2001;5(2):143-156.
33. Pierpaoli C JP, Basser PJ, Barnett A, Di Chiro G. Diffusion tensor MR imaging of the human brain. . *Radiology.* 1996;201(3):637-648.
34. Moscufo N GC, Meier D, et al. Brain regional lesion burden and impaired mobility in the elderly. *Neurobiol Aging.* Apr 2011;32(4):646-654.
35. PASS 2008 [computer program]. 2008.
36. *SAS PROC POWER* [computer program]. Cary, NC: SAS Institute.
37. Diggle PJ. An approach to the analysis of repeated measurements. *Biometrics.* 1988;44(4):959-971.
38. Laird NM WJ. Random-effects models for longitudinal data. . *Biometrics.* 1982;38(4):963-974.
39. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics.* 1982;38(4):963-974.
40. Sliwinski MJ HS, Hall C, Buschke H, Lipton RB. Modeling memory decline in older adults: the importance of preclinical dementia, attrition, and chronological age. . *Psychol Aging.* Dec 2003;18(4):658-671.

13. APPENDIXES

Addendum to Protocol
11 – 01 - 2012

Sleep Assessment:

The relationship between brain white matter disease and sleep will be evaluated using two different instruments which have both been validated in older individuals.

The Epworth Sleepiness Scale (ESS) is a self-administered questionnaire which has been shown to provide a measurement of the subject's general level of daytime sleepiness[1;2]. This 8-item instrument evaluates the extent of subject sleepiness during various normal daytime activities.

The Pittsburgh Sleep Quality Index (PSQI) offers a quantitative assessment of subjective sleep difficulties experienced by each individual[3;4]. The instrument generates "component" scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of scores for these seven components yields one global score[3;4].

The sleep assessments will be administered at baseline, 18- and 36- month timepoints.

Reference List

1. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-545.

2. Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep 1992;15:376-381.

3. Buysse DJ, Reynolds CF, III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193-213.

4. Buysse DJ, Reynolds CF, III, Monk TH, Hoch CC, Yeager AL, Kupfer DJ. Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). Sleep 1991;14:331-338.

Hearing Sub-study Bibliography

1. Fransen E, Lemkens N, Van Laer L, Van Camp G. Age-related hearing impairment (ARHI): environmental risk factors and genetic prospects. Exp Gerontol. 2003;38:353–359.
2. Friedland DR, Cederberg C, Tarima S. Audiometric pattern as a predictor of cardiovascular status: development of a model for assessment of risk. Laryngoscope. 2009 Mar;119(3):473-86.
3. Kaplan RF, Cohen RA, Moscufo N, et al. Demographic and biological influences on cognitive reserve. J Clin Exp Neuropsychol 2009;31:868-76.

4. Musiek, F.E., & Baran, J.A. (2007). The Auditory System: Its Anatomy, Physiology and Clinical Correlates. Boston, MA: Allyn & Bacon.
5. Moscufo, N., Guttmann, C.R., Meier, D., Csapo, I., Hildenbrand, P.G., Healy, B.C., Schmidt, J.A., Wolfson, L., 2011. Brain regional lesion burden and impaired mobility in the elderly. Neurobiology of Aging 32, 646–654.
6. Schuknecht HF. Further observations on the pathology of presbycusis. Arch Otolaryngol. 1964;80:369–382.
7. Vermeer SE, Den Heijer T, Koudstaal PJ, Oudkerk M, Hofman A, Breteler MM. Incidence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Stroke. 2003;34:392–396.
8. Willot, J.F. (1996), Anatomic and physiologic aging: A behavioral neuroscience perspective. Journal of the American Academy of Audiology, 7, 141-151.
9. White WB, Wolfson L, Wakefield DB, Hall CB, et al. Average daily blood pressure, not office blood pressure, predicts progression of cerebrovascular disease and functional decline in older people. Circulation 2011;124:2312-9.