STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official title: Hypertension, intracranial pulsatility and brain Amyloid-beta Clearance (HIPAC) trial

NCT number: NCT03354143

IRB approved date: 10-05-21

Hypertension, intracranial pulsatility and brain Amyloid-beta Clearance

(HIPAC) trial

Funding Sponsor:

National Institutes on Aging (NIA)

Protocol Version 1.0

October 19, 2017

Section 1. Introduction

Mounting evidence indicates that it is the reduction in brain Aβ clearance, rather than its overproduction which is likely to be the underlying mechanism for late-onset AD (>99% cases in the general population).[1, 2] Furthermore, brain Aβ and tau accumulation accelerates age-related cognitive decline, even in cognitively normal older adults.[3-6] The recognized brain Aβ clearance pathways include: **1)** astrocyte phagocytosis and enzymatic degradation of aggregated Aβ;[7] **2)** transportation of soluble Aβ from the interstitial fluid (**ISF**) to CSF with subsequent reabsorption into venous blood and/or the cervical lymphatic system; [8-11] and **3)** direct transportation of Aβ across the blood brain barrier (**BBB**) into the venous blood.[2] At present, the relative contributions of these pathways in brain Aβ and tau clearance remain unknown. A recent study in young and middle aged subjects suggests that direct transport of Aβ across the BBB accounts for ~ 25%, and the CSF reabsorption pathway accounts for another ~ 25% of brain Aβ clearance.[2]

Importantly, the presence of intracranial pulsatility has been recognized as the driving force for brain Aβ and tau clearance through these pathways, and alterations in intracranial pulsatility have been linked to the changes in brain Aβ and tau.[8, 12] However, whether this mechanism functions similarly in humans remains unknown. In this project, we will determine whether changes in intracranial pulsatility alter brain Aβ and tau homeostasis in older adults with hypertension.

Hypertension exacerbates brain atrophy and WMH in older adults.[13-15] Recent studies focus on a neural network-based approach to detect brain changes in hypertension at an early stage.[16-18] For example, disruptions in brain white matter microstructural integrity and neural network functional connectivity were observed prior to the appearance of WMH.[16, 18] Furthermore, a “dose-response” relationship between elevated SBP and reductions in brain white matter integrity has been observed.[16] However, most of these findings are from cross-sectional studies, and it remains to be determined whether intensive BP treatments improve brain white matter integrity and neural network functional connectivity.

In this project, we will determine the effects of intensive antihypertensive treatment on brain white matter integrity and neural network functional connectivity, with a focus on the default-mode neural network (**DMN**) and the frontoparietal network (**FPN**), as these neural networks are sensitive to brain vascular damage, Aβ and tau deposition even before morphological changes such as brain atrophy and WMH.[18-20] To complement these neuroimaging studies, we will use the NIH Toolbox, a well validated test battery, to assess neurocognitive function, with a focus on episodic memory and executive function

which are likely to be affected by hypertension and antihypertensive treatment.[21, 22] Of note, several studies have shown that antihypertensive treatments may prevent or slow progression of WMH in older adults.[23, 24] An ongoing RCT also will determine whether intensive reduction of 24-hour SBP has more benefits on improving neurocognitive function and reducing WMH in older adults (≥75 yrs.) when compared to the standard care.[25] These studies complement this project. However, the aims and outcome measures as well as the study population in these studies are different from this project.

Section 2. Objectives

The overarching goal of this project is to test the hypothesis that intensive antihypertensive treatment alters intracranial pulsatility, which in turn affects brain Aβ and tau protein homeostasis. Furthermore, we will determine whether changes in intracranial pulsatility, Aβ and tau are associated with brain white matter integrity and neural network functional connectivity. To achieve this goal, we will enroll 120 older adults age 55-79. Of those, 40 have normal BP (24- hour BP< 125/75 mmHg) and 80 have high SBP (24-hour SBP ≥125mmHg).[26] Ambulatory 24- hour BP is used because it is a stronger predictor of cerebrovascular disease and cognitive decline in older adults than office BP.[25, 27] Patients with hypertension will be randomized into a 12-month intensive treatment arm (24- hour SBP≤120) and a control arm of the standard care (24-H SBP≤ 130) (1:1) to accomplish the following aims:

Aim 1: Determine the effects of hypertension on intracranial pulsatility, CSF Aβ and tau concentration, brain white matter integrity and neural network functional connectivity. **Hypotheses:** Hypertension is associated with: **1)** augmented central pulsatility, but reduced intracranial pulsatility measured with CINE phase-contrast MRI (**PC-MRI**); **2)** reductions in CSF soluble $A\beta_{42}$, but increases in phosphorylated tau and total tau; **3)** disruptions in brain white matter integrity inferred by diffusion tensor imaging (**DTI**), and functional connectivity by resting-state fMRI (**rs-fMRI**), with a focus on the default-mode neural network (**DMN**) and the frontoparietal network (**FPN**).[18, 20] We will determine whether group differences in intracranial pulsatility, brain Aβ and tau are associated with white matter integrity and functional connectivity.

Aim 2: Determine the effects of intensive BP reduction on intracranial pulsatility, CSF Aβ and tau concentration, brain white matter integrity and neural network functional connectivity. **Hypotheses:** compared to standard care, intensive treatment confers more benefits by: **1)** reductions in central pulsatility, but increases in intracranial pulsatility; **2)** increases in CSF $A\beta_{42}$, but reductions in

phosphorylated tau and total tau; **3)** improvement in brain white matter integrity and functional connectivity.

Section 3. Participant Selection

3.1 Eligibility

The targeted population represents otherwise healthy normotensive and hypertensive adults without cognitive impairment. We will enroll 120 older adults age 55-79. Of those, 40 will have normal BP (24-hour BP<125/75 mmHg) and 80 have high SBP (24-H SBP ≥125). Individuals with and without hypertension will be compared to accomplish **Aim 1** to determine the effects of hypertension on intracranial pulsatility, brain Aβ and tau, white matter integrity and functional connectivity. After baseline measurements, patients with hypertension will be randomized into a 12-month intensive treatment arm (24- hour SBP≤120) and a control arm of the standard care (24- hour SBP≤130) to accomplish **Aim 2** to determine the effects of intensive BP reduction on intracranial pulsatility, brain Aβ and tau, white matter integrity and functional connectivity. Aim 1 and 2 are independent, but highly related to achieve the overarching goal of this project

Table 1. Inclusion and exclusion criteria

Inclusion Criteria
1. Age 55-79, all races/ethnicities, and both genders are eligible;
2. Mini-mental state exam (MMSE) > 26 to exclude cognitive impairment or dementia;
3. Healthy normotensive subjects (24-hour ambulatory BP<125/75 mmHg without use of antihypertensive medication);
4. Patients with hypertension defined as 24-hour SBP ≥125 mmHg , patients on BP medications are eligible;
5. Patients with hypertension are willing to be randomized into either treatment group and ability to return to clinic or laboratory for follow-up visits over 12 months;
6. Fluency in English, adequate visual and auditory acuity to allow neuropsychological testing;
7. Screening laboratory tests and ECG without significant abnormalities that might interfere with the study;

Exclusion Criteria
1. History of stroke, transient ischemic attack, traumatic brain injury or severe cerebrovascular disease by clinical diagnosis or past MRI/CT;
2. Diagnosis of AD or other type of dementia and neurodegenerative diseases;
3. Evidence of severe depression or other DSM-V Axis I psychopathology
4. Unstable heart disease based on clinical judgment (heart attack/cardiac arrest, cardiac bypass procedures within previous 6 months and congestive heart failure), evidence of atrial fibrillation on ECG, or other severe medical conditions;
5. Chronic kidney diseases with GFR < 40 ml/min;
6. Orthostatic hypotension, defined as standing SBP<100 mmHg for hypertensive medicated subjects;
7. History of significant autoimmune disorders such as systemic lupus erythematosus, rheumatoid arthritis and polymyalgia rheumatica;
8. History of drug or alcohol abuse within the last 2 years;
9. Diagnosis of uncontrolled diabetes mellitus (fasting blood sugar ≥126 mg/dL or A1C >7.5%
10. Obstructive sleep apnea;
11. Regularly smoking cigarette within the past year;
12. Severe obesity with BMI $\geq$ 45;
13. Participants enrolled in another investigational drug or device study within the past 2 months;
14. Carotid stent or sever stenosis (> 50%);
15. Pacemaker or other medical device of metal that precludes performing MRI;
16. History of B12 deficiency or hypothyroidism (stable treatment for at least 3 months is allowable);
17. Any conditions judged by the study investigators to be either medically inappropriate, or risky for participant or likely to have poor study adherence.
18. Claustrophobia
19. Pregnancy

Rationale for Exclusion of Certain Study Candidates

Subjects with uncontrolled diabetes mellitus will be excluded because cerebral autoregulation is likely to be impaired in these individuals, which may lead to brain hypo perfusion during intensive lowering of

BP.[28] Reasons for ineligibility and for non-participation of eligible candidates will be recorded in the Study Screening Log.

Inclusion of Women and Minorities

Both women and minorities are included in this study. However, non-English speaking patients will be excluded to allow for the implementation and uniformity of neuropsychological testing which requires fluency in English.

3.2 Recruitment

Recruitment of healthy subjects will be conducted mainly by advertisement in local newspapers and from health fairs and senior centers. We have used these methods successfully to recruit older adults in our previous studies. Recruitment for patient with hypertension will be conducted mainly through the UTSW Medical Center affiliated hospital hypertension clinics. Dr. Vongpatanasin is the director of hypertension section at the UTSW Medical Center. She has regular contact with other hypotension clinicians who will facilitate patient recruitment. Additional recruitment will be conducted via the Texas Health Resource (THR) Hospital Systems, which is the largest health care system in the North Texas and includes 25 major hospitals in the Dallas-Fort Worth area. Dr. Zhang's Cerebrovascular Laboratory is located at the Institute for Exercise and Environmental Medicine(IEEM), which is affiliated with THR. Dr. Zhang has established close collaborations with THR clinicians to conduct clinical studies in hypertension and other chronic diseases in old adults. The experience learned and methods used for patient recruitment will be used in this project. Additionally we will use the Research Registry Database within UTSW Medical Center, social media advertisements, and Craigslist postings.

Adherence and retention: BP treatment effects are monitored during each study visit, and via regular telephone contact. Participants will be asked to return all study medicines and bottles (used and unused) at each visit to monitor compliance. Every effort will be made to provide a friendly clinic environment and to minimize the study burden. Clearly written instructions for each of follow-up visits will be provided and kindly reminded and confirmed with e-mails or phone calls. Time constraints and development of medical conditions are likely to occur in older adults. Study investigators and staff members will work closely with participants to identify and resolve problems if they would occur to enhance adherence. Our previous year-long longitudinal studies in older adults had a 10-15% of dropout rates. We anticipate that we will be able to maintain a similarly dropout rate in this project.

Study protocols and experiment procedures: All study protocols and experimental procedures will conform to the local Institutional Review Board (IRB) requirements as well as ethical considerations for protection of human subjects in clinical studies, and will be approved by the UT Southwestern Medical Center and Texas Health Presbyterian Hospital of Dallas IRB. The information regarding the risks and benefits of the study will be explained to the subjects in lay language. All subjects will be volunteers and will sign an institutionally approved consent form before participating in any experiments. All subjects will complete a health questionnaire and receive a comprehensive physical examination, including 12-lead electrocardiogram prior to participating in the study.

3.3.2 Informed Consent and Screening Visits

Overview of study events - Phone screening: Initial phone screen will assess the key inclusion and exclusion criteria and willingness and suitability for this study. In-person screening will include informed consent, a physical exam including 12 lead ECG, a comprehensive review of medical history and medication, and further evaluation of inclusion and exclusion criteria. Baseline evaluation consists of 2 or 3 visits within ~ 6 weeks to complete all measures (**Table 1**, procedures will be combined as much as possible to reduce visit burden). Control subjects will complete only baseline evaluation. After baseline, patients with hypertension will be randomized to the intervention arms. Follow-up evaluations will be performed at 6 and 12 months to track changes in intracranial pulsatility, brain perfusion, structure and function (**Table 1**). All visits at each follow-up will be completed within a time window of ± 3 weeks. Scheduled in-person and phone checks: Research personnel will meet with the study participants and/or conduct phone assessments to review medication bi-weekly during the first 1-3 months after randomization and monthly afterwards during the whole study period to monitor safety and to enhance compliance. Similar contacts will be made in the standard care and intensive treatment arms.

3.3.2.1 Screening Visits

Screening visits will include: informed consent (also HIPAA & Genetic consents), a physical exam, baseline ECG, and a review of medical history, concomitant medications and a further evaluation of inclusion and exclusion criteria. The in-person screening is anticipated to take a total of 5 hours and may require two visits. Up to 3 weeks are permitted to allow for completion of all screening procedures.

Table 1 Outline of procedures

Procedure	Baseline	6 mo	12 mo
Informed consent	X		
Neuropsychological testing	X	X	X
Structural, functional and CINE PC- MRI	X	X	X
CSF and Blood sample collection	X		X

During screening visits, medical conditions not previously known to the subject or study staff may be identified. If these conditions result in a failure to meet the inclusion and exclusion criteria, those individuals will be considered ineligible for the study. Subjects, who are unable to keep commitments to the screening or baseline visits due to a change in residence location, work or family responsibilities or a loss of transportation will also be considered as ineligible for the study.

3.3.2.2 Screening Visit 1 (SV1)

Informed Consent

The IRB-approved informed consent/HIPAA/genetic consent forms will be provided to and discussed with the participants. Opportunity will be given to ask questions, and answers will be provided by the study coordinator and/or the investigators or the study physicians. The consent forms signed by the participants will be maintained at the PI's laboratory at each site. All study procedures will conform to ethical considerations as approved by the local Institutional Review Boards (IRB) for Human Subjects.

Inclusion/Exclusion Criteria

Review to confirm that all inclusion/exclusion criteria are satisfied. Individuals who meet criteria for enrollment and are willing to be followed longitudinally will be offered the opportunity to participate.

Seated Blood Pressure (BP)

BP will be measured on the right arm (unless a known history of higher left arm blood pressure) at sitting position using a standard automated BP device: Welch Allyn Connex® Vital Signs Monitor series 6000. BP measurements should be taken after resting quietly for > 5 minutes. Three measurements will be performed approximately 1 minute apart. The staff should record all BP measurements. For BP calculation, the staff should discard the 1st measurement and take the average of measurements 2 and 3.

Standing Blood Pressure/Orthostatic hypotension

After sitting blood pressure measurements, participants will be asked to stand up to measure standing blood pressure. The staff will take 3 sequential BP measurements immediately after participant stand. Participants are eligible if there is not a reduction in SBP < 100 mmHg based on the 3rd measurement (may be rescreened if orthostatic hypotension is not accompanied by symptoms of dizziness, pre-syncope or syncope). Normotensive subjects whose standing SBP < 100 mmHg will be included based on clinical judgement of Dr. Vongpatanasin. Data will be recorded in the Form.

Height, Weight and BMI

Height and weight as well as body mass index (BMI) will be obtained according to the procedures in the MOP. Data will be recorded in the history Form.

Mini-Mental State Exam (MMSE)

The MMSE will be conducted as part of the screening eligibility criteria to exclude individuals with gross dementia. [29]

Subjects Demographics

Demographic information will be collected in the history Form.

Subject Concussion History

Subject traumatic brain injury (TBI)/concussion history will be obtained in the history Form.

Subject Medications

Current and history of medication will be collected in the history Form.

Subject Health History

Subject medical history will be collected in the history Form.

Clinical Chemistry

Blood samples (~ 10 ml) will be collected for hematocrit, hemoglobin A1c, and complete metabolic panel. Clinical laboratory tests will be conducted by Quest Diagnostics, serving as a central clinical chemistry laboratory.

Physical/Neurological Exam

A medically qualified professional will perform a complete physical and neurological exam. Data from these exams will be recorded in the HIPAC Trial Screening Visit Form.

Electrocardiogram (ECG)

A12-lead ECG will be performed and interpreted by Dr. Vongpatanasin to assess the presence of cardiac rhythms/atrial fibrillation, ischemic cardiac disease, history of myocardial infarction and/or left ventricular hypertrophy.

Urine Specimen

24-hour urine collection will be collected to measure sodium, phosphate, and magnesium intake.

3.3.3 Baseline Visits

The baseline visit should be completed in 3-4 visits and all the procedures must be completed within a 6-week time period. Neuropsychological testing should not be done the same day as a fasting blood draw.

The MRI should not be performed with fasting; therefore, staff must provide participants snacks prior to initiating the MRI if paired with fasting blood draw.

Neuropsychological Testing and Questionnaires

- Neurocognitive function will be assessed using the NIH-Toolbox Cognition Battery.[21, 30, 31]
- Patient Reported Outcomes of physical and mental health, cognition and health-related QLF will be assessed using NIH PROMIS instruments.

Clinical Chemistry

Fasting blood samples will be collected for the measurements of basic metabolic (BMP), lipid panel, magnesium level, and phosphorous level. Clinical laboratory tests will be conducted by the Quest Diagnostics.

Symptom Check: Clinical symptoms such as dizziness, headaches or back pain will be documented.

Magnetic Resonance Imaging (MRI)

MRI of brain structure and function will be performed at baseline and after 1 years or when subjects drop out from the study. MRI is a required procedure for all study participants during the eligible screen process and consent.

Transcranial Doppler (TCD) Autoregulation/Vascular function

TCD and/or color coded duplex ultrasonography will be used to assess cerebral autoregulation and cardiovascular function. Non-invasive arterial blood pressure, near infrared spectroscopy (NIRS), tonometry and respiratory carbon dioxide (CO_2) using capnography will be used to measure changes in brain blood flow, tissue oxygenation and arterial stiffness. Cerebral autoregulation and cardiovascular function will be assessed. Participants will avoid caffeine, strenuous exercise, and alcohol 24 hours prior to testing. Additionally, they will fast two hours prior to TCD appointment.

3.4 Randomization and Orientation Visit (Day 0)

Hypertensive subjects will be randomized to one of two study arms and stratified by age and sex using a constant blocking factor. Randomization will be conducted by a statistician at UTSW. For treatment assignment, research staff will enter subject identification and stratification information for randomization.

3.4.1 Blinded Research Personnel

Study personnel performing outcome assessments will be blinded to group assignment. The statistician performing primary data analysis will also be blinded. Intervention staff, site safety officers, and individuals not involved in outcome measures will be considered unblinded in order to address safety concerns or adverse events.

In case of an emergency, Dr. Vongpatanasin will determine if unbinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a decision. If an investigator or site staff performing assessments is unblinded, the subject may remain in the study after obtaining approval from the site PI and the reason(s) for making such a decision will be documented.

3.4.2 Randomization and Study Arms

Hypertensive subjects will be randomized into one of 2 study arms (**The standard care arm** and **intensive treatment arm**). BP target for the standard care group is chosen to be 24-hr SBP≤130 mmHg, equivalent to a clinic SBP≤140 mmHg. The 24h SBP target for intensive arm is 24-hr SBP≤120 mmHg, equivalent to a clinic SBP≤130 mmHg. Only authorized staff will access the subject's randomization scheme and obtain the study arm assignment during the orientation visit. During this visit, the coordinator or designate, will provide the participant with a summary of information regarding their group assignment and will schedule the first visit with the intervention staff based on the participant's assigned group. The Orientation Visit will be considered Day 0 of the study. All other visits will be scheduled from this date forward.

Section 4. Interventions/First Orientation Visit

4.1 Standard Care

Subjects in the standard care group will receive the same antihypertensive drug regimen as the intensive BP group in order to minimize potential drug effects on the study outcome. the BP target for the standard care group is chosen to be 24-H SBP≤130 mmHg, equivalent to a clinic SBP≤140 mmHg (Figure 1).[25, 26] Participants in this group may or may not be on treatment with one or more antihypertensive medications at the initial visit. Participants on different antihypertensive drugs are eligible during enrollment. They will be switched to the medications used in this project after baseline measurement.

All clinical visits will be the same for the two groups. We will titrate antihypertensive drugs according to the protocol to achieve 24-Hr SBP to ≤130 mmHg (Figure 1). At each visit, participants will be asked about changes in medications. The study clinician may add, increase or reduce the dose, stop, or change antihypertensive drugs to reach the goal of lowering 24-Hr SBP to < 130 mmHg or clinic SBP <140 mmHg. To minimize subject discomfort during titration of antihypertensive medications, 24-Hr ambulatory BP (ABP) will not be obtained during all clinic visits but will be used to verify if the SBP reaches goal when clinic SBP is < 140 mmHg, unless participants are suspected to have significantly lower out-of-office BP than clinic BP.

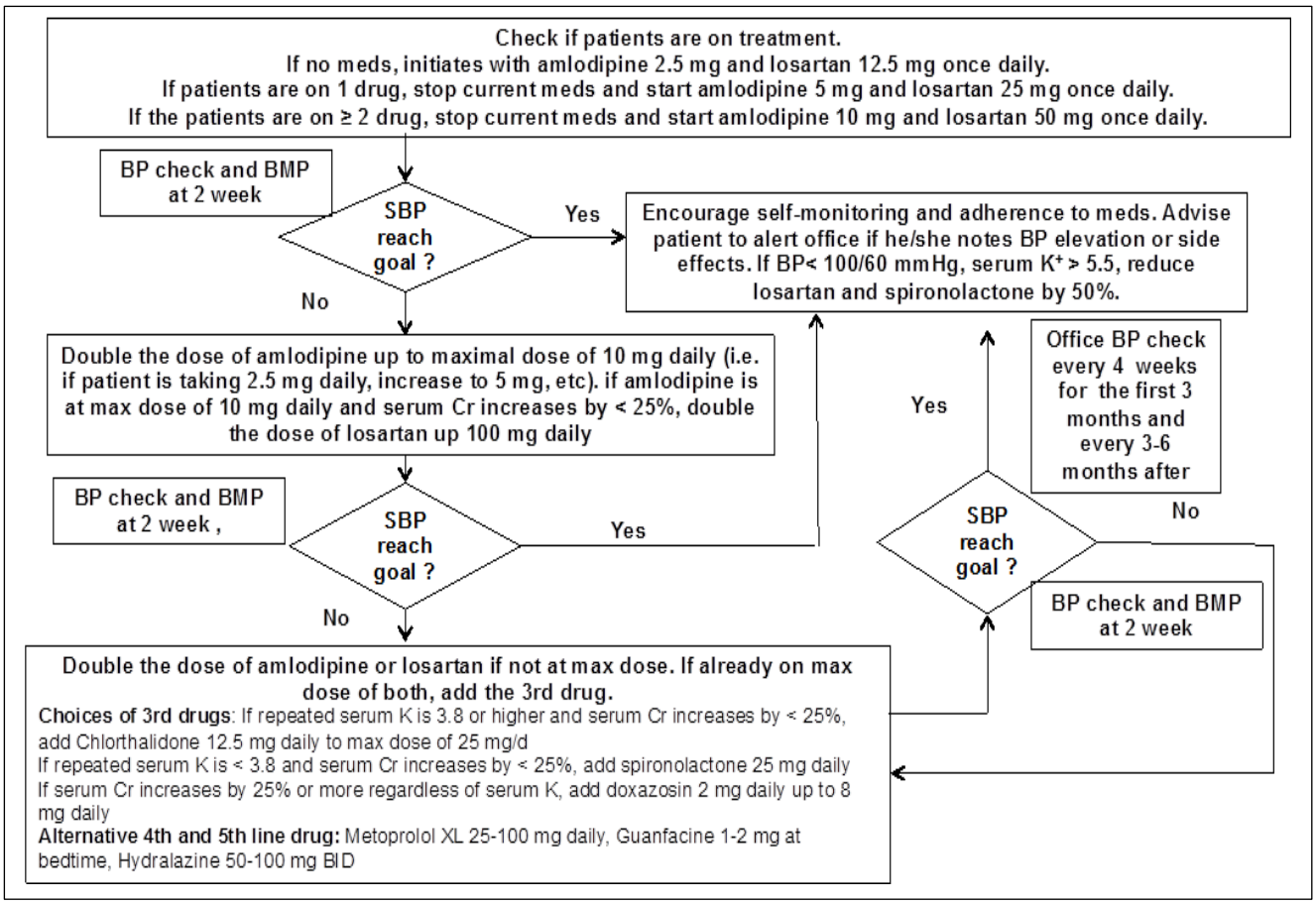
4.2 Intensive Treatment

We will titrate antihypertensive drugs according to the protocol to achieve 24-H SBP to < 120 mmHg, which is equivalent to a clinic SBP<130 mmHg (Figure 1). Calcium channel blocker (CCB, amlodipine) and angiotensin II receptor blocker (ARB, losartan) will be used as the first line antihypertensive to treat hypertension; low dose chlorthalidone diuretic, potassium-sparing diuretic spironolactone, or doxazosin will be added if needed to reach the BP goal.

The study clinician may add, increase or reduce the dose, stop, or change antihypertensive drugs to reach the goal of lowering 24-Hr SBP < 120 mmHg in the interest of participant safety. To minimize subject discomfort during titration of antihypertensive medications, 24-Hr ambulatory BP (ABP) will not be obtained during all clinic visits but will be used to verify if the 24-Hr SBP reaches goal when clinic SBP is < 130 mmHg, unless participants are suspected to have significantly lower out-of-office BP than clinic BP.

4.2.1 Post Randomization (day 0)

Figure1. Hypertension Treatment Algorithm



1) If 24-Hr SBP is ≥130 mmHg while not on any BP meds, start amlodipine 2.5 mg and losartan 12.5 mg once daily.
2) If 24-Hr SBP is ≥130 mmHg while on 1 antihypertensive medication, stop current meds and start amlodipine 5 mg and losartan 25 mg once daily.
3) If 24-Hr SBP is ≥130 mmHg while on 2 or more antihypertensive medications, stop current meds and start amlodipine 10 mg and losartan 50 mg once daily.

NOTE: Doses of amlodipine and losartan may change based on a clinical judgment

4) Schedule Subject's BP and Quest lab test for the 2 week Post Randomization follow up visit (i.e., 2 weeks from starting BP medication).
5) Document all information including visit BP, previous treatment and reason for changing medical regimen or drug dosing in the case report form

Patient Reminders

1) Instruct subjects to take their current dose of BP and all other medications on the day of their next visit so that drug dosing can be titrated accurately at their next visit.
2) Instruct subjects to bring pill bottles, empty or not, to their next visit.

4.2.2. 2 Weeks Post Randomization

Obtain random blood draw for basic metabolic panel and seated/standing BP measurement.

Blood Pressure Management

1) If clinic SBP is still above target (≥140 mmHg for standard arm and ≥130 mmHg for intensive arm), double the dose of amlodipine up to maximal dose of 10 mg daily (e.g., if patient is taking 2.5 mg daily, increase to 5 mg; if patient is taking 5 mg daily, increase to 10 mg).
2) If subject is taking maximal dose of amlodipine (10 mg) and repeated serum K is < 5.0 and serum creatinine (Cr) increases by < 25% from baseline (screening) lab results, double the dose of losartan up to maximal dose of 100 mg daily,(e.g., if patient is taking 25 mg daily, increase to 50 mg; if patient is taking 50 mg daily, increase to 100 mg).
3) If clinic SBP is still above target (≥140 mmHg for standard arm and (≥130 mmHg for intensive arm) and patient is already taking maximal dose of amlodipine (10 mg) plus losartan 100 mg daily or serum Cr increases by at least 25% from baseline (screening) lab results while on less than maximal dose of losartan, add a THIRD drug from the following choices:

- **If serum Cr** increases by 25% or more from baseline (screening) lab results regardless of serum K, add **doxazosin 2 mg daily**.
- **If repeated serum K** is ≥ 3.8 and serum Cr increases by < 25%, add **Chlorthalidone 12.5 mg daily.**
- **If repeated serum K** is < 3.8 and serum Cr increases by < 25%, add **spironolactone 25 mg daily.**

4) If clinic SBP reaches target goal (<140 mmHg for standard arm and <130 mmHg for intensive arm), obtain 24-Hr ambulatory BP monitoring to confirm. If 24-Hr SBP does not reach goal (<130 mmHg for standard arm and < 120 mmHg for intensive arm), use the same protocol for BP titration based on corresponding clinic SBP from 1-3.

Electrolyte Management:

1) **If serum K** is between 5-5.5, stop K supplement (if applicable) and reduce losartan and spironolactone by 50%.

2) **If K** is between 5.5-5.9, hold losartan and spironolactone until K+ <4.8, then consider resuming at 50% reduced dose.

Repeat basic metabolic panel in 2 weeks. If needed, increase or add another BP 9medication to control BP (amlodipine 5-10 mg once daily, doxazosin 4-8 mg once daily, hydralazine 25-100 BID either alone or in combination).

3) **If serum K is ≥ 6.0mmol/L**, subjects should visit emergency department immediately for further management to avoid life threatening arrhythmia.

4) **If serum Cr** increases ≥ 50% from the baseline (screening), hold losartan, spironolactone, and chlorthalidone and repeat basic metabolic panel in 2 weeks. Increase or add other BP medication to control BP, if needed (amlodipine 5-10 mg once daily, doxazosin 4-8 mg once daily, hydralazine 25-100 BID, either alone or in combination).

5) **If serum Na** is < 132 or K < 3.0, reduce chlorthalidone by 50% (i.e. if patient is taking 25 mg daily, reduce to 12.5 mg. if patient is taking 12.5 mg daily, then stop chlorthalidone).

6) **If serum K** is between 3.0-3.5, start KCl supplement 40 meq daily and repeat basic metabolic panel in 2 weeks.

7) **If serum K** is between 2.5-2.9, start KCl supplement dose 40 meq BID, stop chlorthalidone and any thiazide diuretics, and repeat basic metabolic panel in 1 week.

8) **If serum K** is <2.5 mmol/L, subjects should visit emergency department immediately for intravenous K supplement and for further management to avoid life threatening arrhythmia.

The dose of K supplement may be individualized according to clinical judgment.

Management of Low BP/Orthostatic Symptoms

If average seated systolic BP (SBP) < 100 mmHg or the third standing systolic BP is < 90 mmHg or orthostatic symptoms (dizziness upon standing, near fainting, or syncope) are reported, reduce doxazosin and/ or losartan by 50%.

Refill antihypertensive drugs according to the BP and lab results. Lab results may not be available at the time of visit. However, only Losartan, diuretics (chlorthalidone and spironolactone), and potassium

supplement require lab results before intensification for treatment is allowed. Other medications (amlodipine, doxazosin, hydralazine, metoprolol, and guanfacine) may be intensified without lab results if needed.

Subjects should be told that they will be contacted by phone regarding the dose of losartan, diuretics or potassium pills based on lab tests (serum K and Cr). They may be required to return to pick up new bottles of losartan, diuretics or potassium pills the next day or within the same week their lab results are available. However, a BP check is not necessary when subjects return to pick up new medications.

Glycemic control

If plasma glucose is ≥ 140 mg/dL for fasting level or ≥ 200 mg/dL for postprandial level, refer subject to PCP.

Patient Management

1) Schedule Patients to return for 1 month post randomization follow up visit regardless of BP.

2) Instruct participant to take current doses of BP and diabetic medications on the day of their next visit.

3) Instruct patients to bring pill bottles, empty or not, back to their next visits.

Visit Documentation

In the subject's study chart, document the following:

1. Current dose of antihypertensive medication and diabetic medications
2. BP
3. Lab results
4. Previous treatment and the reason for changing medical regimen or drug dosing in the case report form
5. Progress note
6. if the criteria for safety alerts listed below have been met. Site clinicians will be notified within 48 hours so that action may be taken.

- Serum sodium <130 mmol/liter
- Serum sodium >150 mmol/liter
- Serum potassium <3.0 mmol/liter
- Serum potassium >5.5 mmol/liter
- Orthostatic hypotension (based on the third standing systolic BP of < 90 mmHg either with or without dizziness).
- Incident CKD (Increase in serum Cr by at least 50% since the last study lab, usually 3-6 months apart).
- Heart rate < 40 bpm or evidence of new AV block or bundle branch block.

7. Research personnel also perform and document pill count of BP meds to ensure compliance in the case report form.

4.2.3. 4 Weeks Post Randomization (Month 1)

Obtain random blood draw for basic metabolic panel and seated/standing BP measurement.

Blood Pressure Management

1) If clinic SBP is still above target (≥140 mmHg for standard arm and ≥130 mmHg for intensive arm), double the dose of amlodipine up to maximal dose of 10 mg daily (e.g., if patient is taking 2.5 mg daily, increase to 5 mg; if patient is taking 5 mg daily, increase to 10 mg).
2) If clinic SBP is still above target (≥140 mmHg for standard arm and ≥130 mmHg for intensive arm) and subject is already taking maximal dose of amlodipine (10 mg) and repeated serum K is < 5.0 and serum Cr increases by < 25% from baseline (screening) lab results, double the dose of losartan up to maximal dose of 100 mg daily.
   (e.g., if subject is taking 25 mg daily, increase to 50 mg; if subject is taking 50 mg daily, increase to 100 mg).
3) If clinic SBP is still above target (≥140 mmHg for standard arm and ≥130 mmHg for intensive arm), and subject is already taking maximal dose of amlodipine (10 mg) plus losartan 100 mg daily, or serum Cr increases by at least 25% from baseline (screening) lab results while on less than maximal dose of losartan, add the THIRD drug from the following choices:

   - **If serum Cr** increases by 25% or more from baseline (screening) lab results regardless of serum K, add **doxazosin 2-4 mg daily**.

- **If repeated serum K** is ≥ 3.8 and serum Cr increases by < 25% from baseline (screening) lab results, add **Chlorthalidone 12.5 - 25 mg daily.**
- **If repeated serum K** is < 3.8 and serum Cr increases by < 25% from baseline (screening) lab results, add **spironolactone 25 mg daily**.

4) If clinic SBP reaches target goal (<140 mmHg for standard arm and <130 mmHg for intensive arm) and participant has not had ambulatory BP monitoring during previous visit, obtain 24-Hr ambulatory BP monitoring to confirm. If 24-Hr SBP does not reach goal (<130 mmHg for standard arm and < 120 mmHg for intensive arm), use the same protocol for BP titration based on corresponding clinic SBP from 1-3.

Electrolyte Management

Electrolyte management should follow the same principles as above for 2 Weeks
Post Randomization.

Management of Low BP/ Orthostatic Symptoms

If average seated systolic BP (SBP) < 100 mmHg or the third standing systolic BP is < 90 mmHg or orthostatic symptoms (dizziness upon standing, near fainting, or syncope) are reported, reduce doxazosin and/ or losartan by 50%.

Refill antihypertensive drugs according to the BP and lab results. Lab results may not be available at the time of visit. However, only Losartan, diuretics (chlorthalidone and spironolactone), and potassium supplement require lab results before intensification for treatment is allowed. Other medications (amlodipine, doxazosin, hydralazine, metoprolol, and guanfacine) may be intensified without lab results if needed.

Subjects should be told that they will be contacted by phone regarding the dose of losartan, diuretics or potassium pills based on lab tests (serum K and Cr). They may be required to return to pick up new bottles of losartan, diuretics or potassium pills the next day or within the same week their lab results are available. However, a BP check is not necessary when subjects return to pick up new medications.

Glycemic Control

If plasma glucose is ≥ 140 mg/dL for fasting level or ≥ 200 mg/dL for postprandial level, refer subject to PCP.

Patient Management

1) **If BP meds are changed** at this visit, schedule Participant to return for follow up at Week 6 post randomization. **If BP medications are not changed**, schedule Week 8 visit, regardless of BP.
2) Instruct participant to take current doses of BP and diabetic medications on the day of their next visit,
3) Instruct patients to bring pill bottles back to their next visit.

Visit Documentation

In the subject's study chart, document the following:

1. Current dose of antihypertensive medication and diabetic medications
2. BP
3. Lab results
4. Previous treatment and the reason for changing medical regimen or drug dosing
5. Progress note.
6. AE form if the criteria for safety alerts listed below have been met. Site clinicians will be notified within 48 hours so that action may be taken.

- Serum sodium <130 mmol/liter
- Serum sodium >150 mmol/liter
- Serum potassium <3.0 mmol/liter
- Serum potassium >5.5 mmol/liter
- Orthostatic hypotension (based on the third standing systolic BP of < 90 mmHg either with or without dizziness).
- Incident CKD (Increase in serum Cr by at least 50% since the last study lab, usually 3-6 months apart).
- Heart rate < 40 bpm or evidence of new AV block or bundle branch block.

7. Research personnel also perform and document pill count of BP meds to ensure compliance in the case report form.

4.2.4. 6 Weeks Post Randomization

Obtain seated/standing BP only if BP medications are adjusted during the 4-week visit. Obtain a random blood draw for basic metabolic panel only if losartan or diuretics (chlorthalidone or spironolactone) were added or increased at the last visit.

Blood Pressure Management

1) If clinic SBP is still above target (≥140 mmHg for standard arm and ≥130 mmHg for intensive arm), double the dose of amlodipine up to maximal dose of 10 mg daily (e.g., if patient is taking 2.5 mg daily, increase to 5 mg; if patient is taking 5 mg daily, increase to 10 mg).
2) If clinic SBP is still above target (≥140 mmHg for standard arm and ≥130 mmHg for intensive arm) and subject is already taking maximal dose of amlodipine (10 mg) and repeated serum K is < 5.0 and serum Cr increases by < 25% from baseline (screening) lab results, double the dose of losartan up to maximal dose of 100 mg daily.
   (e.g., if subject is taking 25 mg daily, increase to 50 mg; if subject is taking 50 mg daily, increase to 100 mg).
3) If clinic SBP is still above target (≥140 mmHg for standard arm and ≥130 mmHg for intensive arm) and subject is already taking maximal dose of amlodipine (10 mg) plus losartan 100 mg daily, OR serum Cr increases by at least 25% from baseline (screening) lab results while on less than maximal dose of losartan, add the THIRD drug from the following choices:
   - **If serum Cr** increases by ≥ 25% from baseline (screening) lab results regardless of serum K, add **doxazosin 2-4 mg daily**.
   - **If repeated serum K** is ≥ 3.8 and serum Cr increases by < 25% from baseline (screening) lab results, add **Chlorthalidone 12.5 - 25 mg daily.**
   - **If repeated serum K** is < 3.8 and serum Cr increases by < 25% from baseline (screening) lab results, add **spironolactone 25 mg daily**
4) If clinic SBP is still above target (≥140 mmHg for standard arm and ≥130 mmHg for intensive arm) and patient is already taking 3-drug regimen, intensify the THIRD drug by doubling the dose (i.e., increase Chlorthalidone to 25 mg daily, add spironolactone 25 mg daily, or doxazosin up to 8 mg daily)
5) If clinic SBP reaches target goal (<140 mmHg for standard arm and <130 mmHg for intensive arm) and participant has not had ambulatory BP monitoring during previous visit, obtain 24-Hr ambulatory BP monitoring to confirm. If 24-Hr SBP does not reach goal (<130 mmHg for standard arm and < 120 mmHg for intensive arm), use the same protocol for BP titration based on corresponding clinic SBP from 1-3.

Electrolyte Management

Electrolyte management should follow the same principles as above for 2 Weeks Post Randomization.

Management of Low BP/ Orthostatic Symptoms

If average seated systolic BP (SBP) < 100 mmHg or the third standing systolic BP is < 90 mmHg or orthostatic symptoms (i.e., dizziness upon standing, near fainting, or syncope) are reported, reduce doxazosin and/ or losartan by 50%.

Refill antihypertensive drugs according to the BP and lab results. Lab results may not be available at the time of visit. However, only Losartan, diuretics (chlorthalidone and spironolactone), and potassium supplement require lab results before intensification for treatment is allowed. Other medications (amlodipine, doxazosin, hydralazine, metoprolol, and guanfacine) may be intensified without lab results if needed.

Subjects should be told that they will be contacted by phone regarding the dose of losartan, diuretics or potassium pills based on lab tests (serum K and Cr). They may be required to return to pick up new bottles of losartan, diuretics or potassium pills the next day or within the same week their lab results are available. However, a BP check is not necessary when subjects return to pick up new medications.

Glycemic Control

If plasma glucose is ≥ 140 mg/dL for fasting level or ≥ 200 mg/dL for postprandial level, refer subject to PCP.

Patient Management

1) Instruct participant to take current doses of BP and diabetic medications on the day of their next visit,

2) Instruct patients to bring pill bottles back to their next visit.

Visit Documentation

In the subject's study chart, document the following:

1. Current dose of antihypertensive medication and diabetic medications

2. BP
3. Lab results
4. Previous treatment and the reason for changing medical regimen or drug dosing in case report form
5. Progress note.
6. AE form if the criteria for safety alerts listed below have been met. Site clinicians will be notified within 48 hours so that action may be taken.

- Serum sodium <130 mmol/liter
- Serum sodium >150 mmol/liter
- Serum potassium <3.0 mmol/liter
- Serum potassium >5.5 mmol/liter
- Orthostatic hypotension (based on the third standing systolic BP of < 90 mmHg either with or without dizziness).
- Incident CKD (Increase in serum Cr by at least 50% since the last study lab, usually 3-6 months apart).
- Heart rate < 40 bpm or evidence of new AV block or bundle branch block.

7. Research personnel also perform pill count of BP meds to ensure compliance and document on the case report form.

4.2.5. 8 Weeks Post Randomization (Month 2) & Month 3, 6, 9, and 12

1) Obtain random BMP regardless of previous test results. BMP should be obtained at 2, 3, 6, 9, and 12 months and as needed when BP meds are adjusted. 24-Hr ABP should be obtained as soon as clinic BP reaches goal, 6 months and 12 months.

2) Obtain seated and standing BP even if BP was well-controlled at previous visits.

BP Management

1) If clinic SBP is still above target (≥140 mmHg for standard arm and ≥130 mmHg for intensive arm) and patient is already taking maximal dose of amlodipine of 10 mg plus losartan 100 mg daily, or serum Cr increases by at least 25% from baseline (screening) lab while on less than maximal dose of losartan, add a THIRD drug. Choices of third drugs are:

- **If serum Cr** increases by ≥ 25% from baseline (screening) lab results regardless of serum K, add **doxazosin 2 mg daily**.
- **If repeated serum K** is ≥ 3.8 and serum Cr increases by < 25% from baseline (screening) lab results, add **Chlorthalidone 12.5 mg daily.**
- **If repeated serum K** is < 3.8 and serum Cr increases by < 25% from baseline (screening) lab results, add **spironolactone 25 mg daily**

2) If clinic SBP is still above target (≥140 mmHg for standard arm and ≥130 mmHg for intensive arm) and patient is already taking 3-drug regimen, intensify the THIRD drug by doubling the dose (i.e. increase Chlorthalidone to 25 mg daily, add spironolactone to 25 mg daily, or doxazosin up to 8 mg daily).

3) If clinic SBP is still above target (≥140 mmHg for standard arm and ≥130 mmHg for intensive arm) and patient is already taking 3-drug regimen at the maximal tolerated dose, add the fourth drug from the list of third-line drugs that patients have not taken (i.e., combined spironolactone with chlorthalidone or doxazosin, depending on serum K and Cr).

4) If clinic SBP is still above target (≥140 mmHg for standard arm and ≥130 mmHg for intensive arm) despite adding additional drugs from the list of third-line drugs (spironolactone or chlorthalidone or doxazosin), consider adding more drugs from the alternative Fourth- and Fifth-line drug below:

- Metoprolol XL 25-100 mg daily only if HR ≥65 beats/min
- Guanfacine 1-2 mg at bedtime
- Hydralazine 25-100 mg BID

5) If BP goal cannot be achieved with 5 drug regimen, make sure that patient:

1. Is truly adherent to treatment as more than 50% of patients with resistant hypertension are non-adherent to at least 1 drug prescribed in clinical practice.
2. Follows low sodium diet of <1,500 mg/day which could result in as much as 15-20 mmHg reduction in BP in resistant hypertension. See Sodium section.
3. Avoids concomitant medications that may either reduce antihypertensive drug efficacy (e.g., NSAID) or directly increase BP (e.g., glucocorticoids, nasal decongestant or sympathomimetic drugs). See Section 9.9 Concomitant Medications.

A decision will be made whether to exclude the subject from the study and refer for follow up with his/her regular healthcare provider.

Electrolyte Management

Electrolyte management should follow the same principles as above for 2 Weeks Post Randomization.

Management of Low BP/ Orthostatic Symptoms

If average seated systolic BP (SBP) < 100 mmHg or the third standing systolic BP is < 90 mmHg or orthostatic symptoms (i.e., dizziness upon standing, near fainting, or syncope) are reported, reduce doxazosin and/ or losartan by 50%.

Refill antihypertensive drugs according to the BP and lab results. Lab results may not be available at the time of visit. However, only Losartan, diuretics (chlorthalidone and spironolactone), and potassium supplement require lab results before intensification is allowed. Other medications (amlodipine, doxazosin, hydralazine, metoprolol, and guanfacine) may be intensified without lab results if needed.

Subjects should be told that they will be contacted by phone regarding the dose of losartan, diuretics or potassium pills based on lab tests (serum K and Cr). They may be required to return to pick up new bottles of losartan, diuretics or potassium pills the next day or within the same week their lab results are available. However, a BP check is not necessary when subjects return to pick up new medications.

Glycemic Control

If plasma glucose is ≥ 140 mg/dL for fasting level or ≥ 200 or above mg/dL for postprandial level, instruct subject to visit his/her PCP.

Patient Management

1) Instruct participants to take current doses of BP and diabetic medications on the day of their next visit,
2) Instruct subjects to bring pill bottles back to their next visit.
3) Schedule subjects to return for week 8, and at 3, 6, 9, and 12 month visit, regardless of BP.

4) During these visits, obtain a basic metabolic panel, if any diuretics (Chlorthalidone or spironolactone) have been added to the regimen or the dose of diuretics or losartan have been increased. Complete a case report form to document the lab check visit.

Visit Documentation

In the subject's study chart, document the following:

1. Current dose of antihypertensive medication and diabetic medications
2. BP
3. Lab results
4. Previous treatment and the reason for changing medical regimen or drug dosing in the case report form.
5. Progress note
6. AE form if the criteria for safety alerts listed below have been met. Site clinicians will be notified within 48 hours so that action may be taken.

    - Serum sodium <130 mmol/liter
    - Serum sodium >150 mmol/liter
    - Serum potassium <3.0 mmol/liter
    - Serum potassium >5.5 mmol/liter
    - Orthostatic hypotension (based on the third standing systolic BP of < 90 mmHg either with or without dizziness).
    - Incident CKD (Increase in serum Cr by at least 50% since the last study lab, usually 3-6 months apart).
    - Heart rate < 40 bpm or evidence of new AV block or bundle branch block.

7. Research personnel also perform pill counts of BP meds to ensure compliance and document on the pill count in case report form.

4.2.6. 12 Months Post Randomization

1) Obtain seated and standing BP even if BP has been well controlled at previous visits.
2) Obtain fasting blood draw after an overnight fast (9-12 hours) for Complete Metabolic Panel and 24-Hr ABP.

BP, Electrolyte Management, Glycemic Control

BP, electrolyte management, and glycemic control should follow procedures described in 8 Weeks Post Randomization (Month 2) & Month 3, 6, 9, and 12.

Use the AE form to document additional information regarding AST and ALT from complete metabolic panel IF:

Measure	Alert Value
Serum sodium	< =130 or >150 mEq/L
Serum potassium	<3.5 or >5.0 mEq/L
Serum creatinine	Increase by at least 50% since the last study lab (usually 6 months apart).
Serum AST	Increase by at least 2-fold since the last study lab
Serum ALT	Increase by at least 2-fold since the last study lab
CK	Increase by at least 5-fold since the screening lab, with or without muscle symptoms
Heart rate	<40 beats/min (bpm)
Orthostatic Hypotension	The third standing systolic BP is < 90 mmHg

4.3 Milepost Visits

"Clinical inertia" in hypertension management, where clinicians fail to intensify therapy despite patients not being at goal BP, has been observed in both clinical practice and clinical trial settings. For this reason, "Milepost Visits" were used in the intensive BP group in the ACCORD and SPRINT trials to assist in reaching goal SBP. For all participants Milepost Visit date will be assigned at 6 months.

Between these dates, antihypertensive medications should be adjusted and/or additional antihypertensive medications should be added within the recommended dose range to achieve the target BP. However, **once a milepost date has been reached and the participant's 24-SBP is not under target goal, the investigator is required to add to the existing regimen another antihypertensive drug from a drug class different from what is being taken, unless there are compelling reasons to wait. The participant should be seen monthly until the clinic SBP reaches goal.**

If the investigator believes that the ***addition of another drug may potentially be harmful to the participant, the requirement may be waived***. This exception must be justified and documented on the case report form and reviewed by Dr. Vongpatanasin.

4.5 Diastolic Blood Pressure Treatment

The primary BP goal is SBP < 130. Once the SBP goal is achieved, the antihypertensive regimen should be intensified to achieve 24-Hr DBP < 80 mmHg for standard arm and < 70 mmHg for intensive arm. If clinic DBP remains ≥ 95 mmHg at a single visit or ≥ 90 mmHg at two successive visits, antihypertensive treatment should be intensified. The visit intervals and decisions for titration (other than the BP levels) will be similar to those used for the SBP goal.

4.6 Drug Dispensing

All study medications dispensed to participants will be labeled with the medication, study and participant's name, strength and quantity, directions for use, and authorized prescriber's name. An emergency study-related phone number for study drug information will also appear on the label. All participants are to be counseled verbally on medication administration. Written instructions will also be provided.

Participants will receive a 30-day medication supply at each regular visit during the first 3 months after randomization. After 3 months, a 90-day supply may be provided to reduce unnecessary visits to the study sites. Medication may be dispensed in the intervening periods between visits in case of emergency, loss, or schedule change. A tracking record is maintained for all dispensing actions. It is recommended that the number of authorized dispensing personnel be limited to assure proper adherence to established accountability and dispensing procedures.

4.7 Drug Storage and Disposal

Clinical Sites are responsible for destroying expired drug and documenting destruction.

4.8 Concomitant Medications

Combinations of RAS blockers (ACE inhibitor, ARB, and/or renin inhibitor) are strongly discouraged in HIPAC, based on lack of benefit and adverse outcomes seen in several large randomized controlled trials.

The use of 2 nodal blockers (**beta blocker** and a non-dihydropyridine calcium channel blocker) is strongly discouraged. Additive reductions in heart rate, cardiac conduction, and cardiac contractility may occur when non-dihydropyridine calcium channel blockers (e.g., verapamil or diltiazem) are used concomitantly with beta blockers. While this combination may be useful and effective in some situations, potentially serious cardiovascular adverse effects such as congestive heart failure, heart block, severe bradycardia, ventricular asystole, and sinus arrest have been reported. If a non-dihydropyridine CCB (e.g., diltiazem) is to be used, it should not be combined with a beta-blocker.

An HIPAC participant who cannot achieve SBP at target goal despite maximal doses of first to fifth line drug therapy outlined may require **Minoxidil** to achieve target BP. Since Minoxidil is a potent vasodilator, participants not receiving adequate doses of a diuretic (usually a loop diuretic with or without a thiazide diuretic) will face a substantial risk of fluid overload. Therefore, whenever a participant is prescribed Minoxidil, additional therapy with either chlorthalidone or a loop diuretic is strongly encouraged. Although the diuretic dose requirement may vary from patient to patient, most patients on Minoxidil will require at least 12.5mg/day chlorthalidone **or loop diuretic equivalent to furosemide** 40 mg/day (usually BID unless prescribed with a thiazide diuretic). Participants on Minoxidil doses above 20 mg/day will require even higher diuretic doses and the need for a combination of a thiazide and loop diuretic is not uncommon. Participants prescribed Minoxidil without also receiving chlorthalidone or a loop diuretic will receive email alerts and messages similar to those described above for discouraged combinations.

The use of **simvastatin** with calcium channel blockers including amlodipine, verapamil, and diltiazem should be avoided due to increased risk of muscle damage (http://Safety Officer .fda.gov/Drugs/DrugSafety/ucm256581.htm). Similarly, simvastatin should not be used at the dose of 80 mg because of increased risk of myopathy. Simvastatin should not be used in HIPAC.

Some prescription or over-the-counter drugs (as shown in the following list) may reduce antihypertensive efficacy of BP medications or directly increase BP. The use of these drugs should be discouraged or minimized as much as possible.

- **NSAIDS** : Ibuprofen (motrin, advil), naproxen (alleve), meloxicam (mobic), high dose aspirin.

- **Sympathomimetics**, including nasal decongestants and ADHD drugs: midodrine, droxidopa, pseudoephedrine, ephedrine, methamphetamine, methylphenidate (Ritalin), dexmethamphetamine
- Immunosuppressive drug: **cyclosporin**
- **Glucocorticoids**: prednisone, dexamethasone (solumedrol), medrol dose pak
- **Drugs to increase red blood cells**: Erythropoietin, Darbepoietin
- **Mineralocorticoids**: fludrocortisone
- **Oral Contraceptives**
- Herbal supplement: **St. John's Wort**

4.9 Medication Adherence

Participants will be asked to return study medication bottles, used and unused, at each visit; pill counts will be performed to monitor compliance. The percentage of pills taken/dispensed will be used to document drug adherence. HIPAC will strive to achieve a goal >80% treatment adherence. Potential effects of intervention adherence on study outcome measures will be assessed as secondary data analysis.

Monthly phone or in-person follow-up and three month clinic visits to monitor study safety and compliance will be conducted with all participants in order to maintain the same level of study contact across all study arms.

4.10 Assessment of Orthostatic Hypotension (OH), Measurement of Standing Blood Pressure

Standing BP will be measured at screening, and all subsequent visits, using the same BP device that is used to measure seated BP. After seated BP measurements, participants will be asked to stand. Beginning when their feet touch the floor, BP will be taken one minute later in the same arm used for the seated measurements. Participants will be asked after the standing BP measurements if they had any symptoms of orthostatic hypotension during the standing BP measurement.

Participants with standing SBP <100 mm Hg will not be eligible for randomization (may be rescreened if corrected). However, the detection of asymptomatic orthostatic hypotension, i.e., orthostatic hypotension unaccompanied by orthostatic symptoms of dizziness, presyncope or syncope will not

influence the antihypertensive drug treatment algorithm. Symptomatic orthostatic hypotension will be managed as follows.

Definition

Orthostatic hypotension (OH) is usually defined as a decline of systolic blood pressure (SBP) ≥20 mmHg or a decline of diastolic BP ≥10 mmHg that occurs within 3 minutes after moving from a supine or seated to a standing position.

Symptoms

OH may be asymptomatic or may be accompanied by dizziness, lightheadedness, feeling faint, or syncope. Generally, asymptomatic OH should not change adherence to the HIPAC protocol, although medication classes may be adjusted to continue appropriate BP control while minimizing postural hypotension (see below Management of OH).

Predisposing Conditions

In epidemiologic studies OH is more likely to occur in older individuals with high SBP. Diabetes mellitus and other autonomic neuropathies, volume depletion, varicose veins, alcoholism, and certain medications are also associated with OH.

Note: Occasionally, hypotension occurs if a patient previously nonadherent to prescribed medications begins taking the medications. Because BP typically declines after a meal due to splanchnic blood pooling, standing BP should not be measured within 90 minutes after a meal if possible.

Predisposing Medications

Some classes of medications are more likely to cause OH than others. The most frequent offenders currently in use are alpha-blocking drugs, such as prazosin, terazosin, or doxazosin, and central alpha agonists, such as clonidine, methyldopa or guanfacine. Although beta-blockers are perhaps the least likely antihypertensive class to cause OH, one of the most common adverse effects of combined alpha-beta blockers, such as labetalol or carvedilol, is OH or dizziness, primarily because of the alpha-blocking component of these drugs. Rarely, beta-blockers may cause OH because of severe bradycardia (e.g., heart rate <40-50 beats/min) and inability to increase heart rate/cardiac output in upright posture, especially if other drugs or conditions have lowered BP excessively. Occasionally, reserpine, nitrates, or

calcium channel blockers may contribute to or cause OH. Certain psychotropic drugs, most notably phenothiazines, can also cause OH.

Thiazide diuretics rarely cause OH, unless the patient is significantly volume depleted or another agent is added to a diuretic that may cause first-dose hypotension (e.g., a short-acting ACE inhibitor like captopril or a short-acting alpha blocker like prazosin). High dose loop diuretics, such as furosemide, or combinations of diuretics may lead to excessive volume depletion and hypotension, with or without OH.

Management of OH

Patients with poor oral intake, dehydration from any cause, GI or renal causes for excessive fluid loss, or hemorrhage, may need to have their diuretic or other antihypertensive medications stopped temporarily until the volume-depletion is corrected. If a participant with symptomatic OH has no obvious cause of excessive volume depletion, the medication regimen should be reviewed. Psychotropic drugs may need to be reduced in dose or changed to alternative agents (many newer ones are equally effective without hypotensive effects). If the patient is on an alpha-blocker, alpha-beta blocker, or central alpha agonist, the dose should be reduced or the potentially offending agent discontinued. If necessary for BP control, that drug should be replaced with another class of antihypertensive that is less likely to cause symptomatic OH. If the participant requires an alpha-blocker for BPH/bladder outlet obstructive symptoms, a more selective alpha-blocker (e.g., tamsulosin) may be considered.

Patients with symptomatic OH should eat small meals and avoid standing up rapidly after eating. Such individuals should avoid hot showers and other excessive heat exposure. An increase in sodium intake may be considered in patients without hypertension or heart failure. In individuals with large varicose veins, fitted elastic hose or compression stockings may reduce venous pooling in the legs. In refractory cases of symptomatic OH, drug therapy with vasoconstrictors such as midodrine or dihydroergotamine or with mineralcorticoids may be considered. This is unlikely to be needed in HIPAC.

Implications for protocol

The presence of orthostatic hypotension, particularly if asymptomatic, should not be considered as an exclusion from the study, particularly since some studies indicate that control of hypertension can lead to improvement in orthostatic hypotension. Likewise, decisions regarding up-titration toward protocol blood pressure targets should be made primarily on the basis of the seated blood pressure measurements. Orthostatic hypotension should also not preclude up-titration toward blood pressure targets. When symptomatic, it is suggested that initial efforts described above should be directed toward

identification of other causes (e.g., psychotropic drugs, recent meal ingestion) and preferential use of hypertension medication classes that have less predilection to orthostatic hypotension.

4.11 Dietary / Lifestyle Modification

Dietary modifications are recommended based both on blood pressure control and prevention of CVD risk factors. The main focus of nutrition intervention for HIPAC participants without chronic kidney disease will be the DASH Diet recommendation. Patients with stage 3 or greater kidney disease will receive alternate dietary instruction. Recommendations will also be made for alcohol intake.

DASH Diet

The DASH diet is an eating plan that is low in saturated fat, cholesterol, and total fat. It emphasizes fruits, vegetables, fat-free or low-fat milk and milk products, and includes whole grain products, fish, poultry and nuts. Red meat, sweets, added sugars and sugar-containing beverages are reduced on the DASH eating plan. The DASH diet is rich in potassium, magnesium and calcium as well as protein and fiber.

HIPAC participants who do not have chronic kidney disease should be introduced to the DASH diet by study coordinators. Each participant will receive a copy of the DASH diet recommendation prepared especially for HIPAC participants at the study enrollment. Study coordinators should review the table that provides the number of daily servings for the DASH eating plan with study participants.

Diet for Chronic Kidney Disease

The DASH diet is high in nutrients and foods which can be detrimental to participants with chronic kidney disease. Participants meeting the criteria for chronic kidney disease should instead be counseled on a prudent renal diet and provided with the National Kidney Foundation educational material (see http://Safety Officer .kidney.org/atoz/index.cfm). Specifically, patients with chronic kidney disease should be counseled to limit foods that are high in phosphorus. They may also need to limit their potassium intake and their intake of protein. Protein-rich foods include red meat, poultry, fish and other seafood, eggs, dairy product and vegetables and grains.

Reduced Sodium Diet

Dietary sodium intake should be reduced to less than 1500 mg/day for the HIPAC study population.

High sodium foods should be avoided, including chips, nuts, lunch meats, most canned foods, most fast foods, pickles and olives. Instead of adding salt to foods for flavor, encourage trying pepper, lemon juice, mustard, garlic, spices, herbs and salt substitutes. Participants with chronic kidney disease should be counseled to discuss use of salt substitutes with their health care provider or clinical nutritionist before using. Many of these products substitute potassium for sodium. Increased potassium intake is not recommended for patients with CKD. Emphasize choosing more fresh foods - vegetables, fruits, grains, meats, and minimally processed foods. Encourage more home preparation of foods and reading food labels to help make lower sodium choices. Examples of diet high in sodium are shown in the table below which should be avoided or minimized.

4.12 Study Drug Supply and Dispensing

4.12.1 Drug Dispensing

Drugs will be labeled and identified with the study name, participant's name, medication name, strength and quantity, directions for use, and authorized prescriber's name. An emergency study-related phone number for study drug information will also appear on the label. All participants are to be counseled verbally on medication administration. Written instructions will also be provided.

Participants will receive a 30-90 day medication supply during each regular visit (the amount of drug dispensing will be site specific). Medication dispensing may occur in the intervening periods between visits in case of emergency, loss, or schedule changes. A tracking mechanism is maintained for all dispensing actions. It is recommended that authorized dispensing personnel be limited in number to assure proper adherence with established accountability and dispensing procedures.

4.12.2 Drug Storage

Research personnel is responsible for storing the study drug supplies in a locked, secure area with limited access. Manufacturer recommendations and local policies for drug storage must be followed.

4.12.3 Drug Disposal

Research personnel is responsible for destroying expired drug and documenting destruction.

4.13 Intervention Compliance and Adherence Monitoring

The randomization procedures will be explained fully to the participants during enrollment and their understanding and willingness to be randomized into one of the 2 study arms will be confirmed. Participants will be encouraged to stay with the interventions they have received. Any changes in the health-related behavior or medication, which may impact study outcome, will be reviewed, discussed and documented during regular study visits.

Treatment effects of BP will be monitored at each study visit. Participants will be asked to return study antihypertensive drug bottles, used and unused, at each visit; pill counts will be performed to monitor compliance. The percentage of pills taken/dispensed will be used to document drug adherence. Potential effects of intervention adherence on study outcome measures will be assessed as secondary data analysis.

Monthly phone or in-person follow-up and three month clinic visits to monitor study safety and compliance will be conducted with all participants in order to maintain a same level of study contact across the study arms. At each visit, participants will be asked about any changes in their medications and health to monitor and record potential influences on study outcome measures.

4.14 Retention Strategies

Every effort will be made to provide a friendly clinic environment for study visits, to foster personal relationships between study staff and participants, and to minimize study burden. Clearly written instructions for follow-up visits will be provided and reminder calls will be made before each study visit.

Section 5. Outcome Measurements and Follow-Up

Post-randomization follow-up schedules for outcome measurements and safety monitoring are summarized in Table 1. Participants will be monitored and interviewed during monthly phone or in-person visits and clinic visits at 6, 9, 12, months for all study arms. All follow-up visits will be completed within a time window of ± 2 weeks. Vital signs, physical exam and laboratory tests will be performed if suggested by clinical symptoms to ensure safety.

5.1 Measurement of Neurocognitive Function

Lowering BP in older adults may slow cognitive decline in episodic memory and processing speed.[14, 33] We will use NIH-Toolbox to assess changes in neurocognitive function which includes: Episodic memory with the Picture Sequence Memory Test; working memory with the List Sorting Working Memory Test; executive function and Attention with the Flanker Inhibitory Control and Attention, and Dimensional Change Card Sort Tests; processing speed with the Pattern Comparison Processing Speed Test.[21] A composite z score will be obtained by conversion of individual test scores to the standardized z scores, then averaged to assess changes in global cognition.[34] Domain specific z scores will be used to assess changes in specific cognitive function associated with hypertension and antihypertensive treatment. Heath-related quality of life will be measured using the NIH PROMIS, a set of highly reliable, precise instruments to assess patient-reported health status for physical, mental, and social well-being . Measurement of neurocognitive function will be performed at Baseline, 6, and 12 months.

5.2 Magnetic Resonance Imaging (MRI)

The MRI methods used in HIPAC trial have been used in our previous studies,[35-38] which have demonstrated strong to excellent test-retest reproducibility, i.e., the intersession coefficient of variation for PC-MRI CBF and CSF flow is ~ 7% and 5%, respectively;[39, 40] DTI metrics, ~ 3%;[41] and the intra-class correlations for DMN functional connectivity is ~ 0.7.[42] We also have extensive experience in CSF sampling and ELISA study of Aβ, tau and inflammatory cytokines in older adults.[32] Blood and CSF sampling, processing and storage and analyses will follow the standard protocols of NIA Biospecimen Best Practice Guidelines). The NIH Toolbox is a sensitive and well validated test battery for cognitive assessment; the test-retest reproducibility, measured as the intraclass correlation coefficient for episodic memory, attention and executive function, which are the focus of this project, ranges from ~ 0.77 to ~ 0.94.[21] Thus, we are confident about the accuracy and reliability of the methods used for the outcome measures proposed in this project.

1) Measurement of intracranial pulsatility using CINE PC MRI We will use the velocity-encoded CINE PC MRI to measure intracranial pulsatility .[38, 43, 44] **2) Quantification of the arterial pressure-CBF coupling relationship** We will use high temporal resolution TCD to measure CBF velocity waveforms at the MCA, and applanation tonometry to measure changes in central arterial pressure at the ICA.[45] Applanation tonometry also will be used to assess central arterial stiffness by measuring the carotid-femoral pulse wave velocity (PWV).[35] Fourier spectral analysis will be used to estimate cerebrovascular

resistance/impedance.[45] Mean blood pressure and CBF velocity will be used to estimate cerebrovascular resistance index (CVRI=BP/CBFV). In addition, we will use 2D color-coded duplex ultrasonography to measure volumetric CBF from the ICA and the vertebral artery (VA) to calculate total CBF and cerebrovascular resistance (CVR=BP/CBF).[46] **3) Quantification of the CBF-brain tissue and CBF-CSF coupling relationship** Collecting CINE PC MRI data in sync with the cardiac cycle, we will measure pulsatile oscillations of CBF at the ICA, brain tissue volume, local brain tissue movements, and CSF dynamic flow at the aqueduct of Sylvius within a whole cardiac cycle**4) Measurement of brain volume, T2 FLAIR WMH and perfusion i)** 3D T1-weighted Magnetization-Prepared-Rapid-Acquisition-of-Gradient-Echo (**3D MPRAGE**) sequence (4 min 48 sec) will be used to measure brain volume **ii**) T2 FLAIR sequence (4 min 12 sec) will be used to measure WMH volume. **iii)** Pseudo-continuous arterial spin labeling (**3D PCASL**) sequence will be used to measure regional CBF.**5) Measurement of brain white matter microstructural integrity and neural network functional connectivity i)** Diffusion tensor imaging (**DTI**) **)** and rs-fMRI will be used to measure neural network functional connectivity.

5.3 Clinical Chemistry

5.3.2 Clinical Chemistry

For all study arms, fasting serum and whole blood will be collected for CMP, lipid profile, hemoglobin A1C and analyzed by Quest Diagnostics at Baseline, 6, and 12 months. BMP also will be performed at the 2 and 4 weeks during the first month, then at the 2, 3, and 9 months or as needed based on clinical judgment/medication adjustment during the trial.

5.4 Concomitant Medications

All concomitant medication taken during the study must be recorded during each study visit. Information regarding participants' concomitant non-study medication therapy is collected and documented at baseline and then reviewed and revised at each follow-up visit. Appropriate sources for obtaining this information include participant (or significant other) report, current pharmacy action profiles, and verification of medications documented in the medical record.

5.5 Discontinuations

5.5.1 Discontinuation of Subjects

Subjects may be discontinued from the intervention, but remain in the study, or may be withdrawn from the study by the investigator for any of the following reasons :

1) Persistently low eGFR of < 15 ml/min/1.73 m2 or serum K^+ > 5.5mmol/L that does not respond to antihypertensive dose reduction or adjustment.

2) Systolic BP equal or greater than 180mmHg and/or diastolic BP equal or greater than 110 mmHg.

3) Comorbidities that make continued participation in the study medically inappropriate or impossible.

4) Significant cognitive decline defined as a decrease in MMSE by 3 points and/or clinical manifestation of confusion, disorientation, problems with judgment or bizarre behavior that may impair subject's safety and/or ability to participate in the study.

5) Subjects may withdraw their consent at any time by notifying study staff.

Any subject who withdraws or is discontinued will be referred to their treating physician/PCP for follow-up during reduction or discontinuation of statins or antihypertensive in order to monitor and resolve any drug-related abnormalities. Subjects who withdraw or discontinue due to significant cognitive decline will be evaluated by the site PI or clinician to determine whether dementia or other diseases are present. Previous cognitive test results will be reviewed and Clinical Dementia Rating (CDR) scale will be used to assist clinical judgment. Subjects who discontinue from the study early will be encouraged to have an early termination visit at the time of discontinuation so that study staff can perform as many outcome measures as possible if judged clinically safe for participants.

5.5.2 Temporary Discontinuations

Antihypertensive drugs may be temporarily discontinued if participants develop low BP (<90/60 mmHg) and renal dysfunction (eGFR reduced by > 50%) related to severe dehydration, nausea, vomiting, diarrhea, reduced oral intake, or febrile illness that may incidentally occur during the trial. BP treatment may be restarted after side effects are reduced and it is judged clinically safe to restart study medication.

5.5.3 Discontinuation of the Study

The study may be discontinued by the IRB, SO, NIH or other government agencies as part of their duties to ensure the protection of research participants. In addition, DSMB may require an interim safety data analysis based on the overall safety profile and AE or SAEs monitoring to make recommendations to the NIH and the PIs concerning discontinuation of the study if the adverse effects during the study period exceed what would be expected under the study treatments (BP reduction) in older adults when compared with similar trials reported previously.

Section 6. Safety Monitoring and Reporting

6.1 Introduction

All antihypertensive agents in the study have been approved by the Food and Drug Administration (FDA) and have been routinely prescribed for lowering BP and blood lipid level in older adults. Patient safety will be monitored carefully beginning from the enrollment and throughout the whole study. Each participating investigator has primary responsibility for the safety of participants under his/her care. In addition, an independent HIPAC Safety Officer (SO) will monitor the study safety and any potential treatment-related adverse events (AEs) and serious adverse events (SAEs) to protect the safety of study participants.

6.2 Safety Monitoring

Several safety issues related to the side effects of antihypertensive agents may be a concern (discussed below). Potential side effects of antihypertensive drugs will be reviewed and discussed with participants during the enrollment. Participants will be asked to inform the study clinician or staff immediately if side effects occur and persist. Participants will be monitored and interviewed during each of the follow-up visits to ensure that any symptoms are addressed early and properly.

Antihypertensive medication

Potential adverse effects of the blood pressure drugs used in HIPAC have been well documented. For example, electrolyte abnormalities (hyponatremia or hypokalemia are known to be associated with thiazide diuretics; hyperkalemia and short-term decline in GFR with losartan, hyperkalemia with spironolactone; as well as bradycardia with beta blockers). Participants will be monitored routinely with interviews, vital signs, targeted physical examination and regular laboratory tests to ensure safety (see Figure 1, Table 2). In addition, site clinicians may also obtain lab tests and/or ECG if safety is a concern at non-scheduled intervals. Clinical alerts are generated when the safety parameters exceed the established thresholds (see Table 2). Expected events associated BP drugs will not be considered as SAEs unless they meet the criteria for a SAE.

Table 2 Clinical Safety Alerts

Measure	**Alert Value**
Serum K^+	> 5.0 mmol/L
Serum K^+ and Na^+	K^+ < 3.5 or Na < 130 mmol/L
Heart rate	Resting HR < 40 beats/min (bpm)
ECG	Evidence of AV or new bundle branch block
SBP	Standing SBP < 90 mmHg or seated SBP < 100 mmHg

6.3 Protection Against Risk

Risk associated with antihypertensive medications: All antihypertensive medications used in the study are approved by the FDA. The side effects and risks are not more than the expected risk in the clinical setting. However, we plan to modify treatment in response to safety concerns as below:

If serum $K^+ > 5.0$ mmol/L:

1. If serum K^+ is between 5-5.5, stop K supplement (if applicable) and reduce losartan and spironolactone by 50%.

2. If K^+ is between 5.5-5.9, hold losartan and spironolactone until $K^+ < 4.8$, then consider resuming at 50% reduced dose. Repeat BMP in 2 weeks. Increase or add other BP medication to control BP if needed (amlodipine 5-10 mg once daily, doxazosin 4-8 mg once daily, hydralazine 25-100 BID either alone or in combination).

3. If serum K^+ is $\geq$ 6.0 mmol/L, patients should visit emergency department immediately for further management to avoid life threatening arrhythmia.

4. Increase or add Amlodipine, Doxazosin, hydralazine, chlorthalidone to control BP, if needed.

5. Recheck BP and BMP 1-2 weeks after drug adjustment.

If serum $K^+ < 3.5$ or serum $Na^+ < 130$ mmol/L:

1. Reduce chlorthalidone dose by 50%.

2. Increase or add other BP medication to control BP, if needed.

3. If serum K^+ is between 3.0-3.5, subjects will receive KCl supplement 40 meq daily and BMP will be repeated in 2 weeks.

4. If serum K^+ is between 2.5-2.9, subjects will receive KCl supplement 40 meq bid, stop chlorthalidone and any thiazide diuretics, and BMP will be repeated in 1 week.

5. If serum K^+ is < 2.5 mmol/L, patients will be asked to visit emergency department immediately for intravenous K supplement for further management to avoid life threatening arrhythmia.

6. Recheck BP and BMP in 1-2 weeks after drug adjustment.

HR < 40 bpm or evidence of AV or new bundle block:

1. Reduce the dose of Beta Blockers by 50%.

2. Increase or add other antihypertensive drugs to control BP, if needed.

3. Recheck BP after drug adjustment.

Standing SBP < 90 mmHg or seated SBP <100 mmHg:

1. Reduce the dose of Doxazosin, or amlodipine, or diuretics or Losartan by 50 %.

2. Recheck seated and standing BP 2 weeks after drug adjustment. If the standing BP continues to be <90, discontinue Doxazosin, or other antihypertensive drugs, as needed.

Magnetic Resonance Imaging

MRI is a safe procedure, used routinely in the clinical evaluation of brain disorders. There are no known risks from exposure of older adults to 3T magnetic fields that will be used in this study. Claustrophobia occurs occasionally in the MRI scanner, but there are no known long-term adverse effects. Usually, conversation and reassurance will remove such anxieties. If subjects experience severe anxiety during MRI, they will be free to end the session at any time. However, metallic objects are hazardous in MRI environment because they can interact and be attracted to the scanner. As a result, each subject will be screened with a standard MRI safety form before each MRI scan to rule out potential safety hazards. A participant who is wearing a pacemaker, neurostimulator, or any other implanted device will not be allowed to participate in MRI. All metallic objects (keys, watches, and the like) will be removed from the researchers and subjects before the MRI experiment begins.

The risk of MRI to pregnant women and unborn babies is not known. For this reason, women who are pregnant are not allowed to enter the scanner environment. Thus female participants will be asked to fill out the pregnancy screening form. We will provide a pregnancy test to each female participant who is unsure if she is pregnant. If participants have a positive pregnancy test, or are not sure whether they are pregnant, but don't want to take the pregnant test, they will not be able to participate in this study.

Phlebotomy Venous catheters are placed for blood sampling

There is a small (<5%) risk of superficial thrombus at the insertion site, and a smaller risk (<2%) of bleeding or infection. To make the blood draw procedure safe and easy for the participants, only trained and experienced Phlebotomist/Nurses will be delegated to perform venipuncture. All measures will be taken to ensure infection prevention.

Questionnaire administration and neuropsychological testing

Every effort will be made by the investigators to minimize the possible risks of psychological and/or physiological discomfort of participants during either interviews or studies by reassurance of the subjects and by offering rest breaks if needed or required. Participants can skip any question that they do not wish to answer and any test that they do not want to perform.

Loss of Confidentiality

The data obtained from this project will be used exclusively for the purpose of the research and will not be identifiable to individual subjects when published. All information obtained that can be identified with an individual subject will remain confidential and will be disclosed only with a subject's permission. We will retain whatever blood and cerebral spinal fluid are left over after all the analyses are complete in case other tests become available that might be useful to explain the effects of aging on the brain. The samples will be kept in the freezer in the Stowe lab at UTSW. All samples will be labeled and coded, with each subject's personal information de-identified. Only the study investigators will have access to these samples. All data collected will be coded with an experiment and subject specific code to maintain confidentiality. Only the members of the research team will be able to access to this coding information. All samples will be kept until the end of the study then de-identified for future research.

Other Risks

Unanticipated problems or side effects of BP lowering drugs that are unknown at this time may be possible. The investigators will make every effort to minimize potential risks of participants experiencing either psychological or physiological discomforts during either interviews or studies by offering reassurance and rest breaks if needed. All study procedures and protocols will be approved by the local IRB and HIPAC Safety Officer (SO).

6.4 Safety Reporting

6.4.1 Adverse Events and Serious Adverse Events

Adverse Event (AE)

Any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

Serious Adverse Event (SAE)

Any adverse event that:

- Results in death
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards

Participants will be queried for AEs and SAEs at regular phone and clinic visits. Information on SAEs may also be reported to study staff by participants at any time between visits.

6.4.2 AE Reporting

All AEs, expected or unexpected, are collected on an Adverse Event Form . All AEs experienced by the participant during the time frame of the study (e.g. screening, baseline, follow-up visits or close-out), under a specific condition and location will be reported. The reporting time frame and procedures will meet the requirements of the local IRB, HIPAC SO and NIA.

6.4.3 SAE Reporting

SAEs will be reported to the UT Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas Institutional Review Boards as soon as the event is known. All SAEs will be recorded by research personnel and forwarded to the Drs. Zhang and Vongpatanasin within 48 hours of knowledge of the event. The PI will notify the Safety Officer and NIA Program Officer within 24 hours of the event being

reported. The SO and NIA will receive notification about all SAEs within 72 hours of when the event is known and reported by study staff. The reporting time frame and procedures to the local IRBs will follow the guidelines of the local IRB. SAEs will be collected and reported from screening to the end of the study follow-up period for an individual participant. SAEs will be followed until resolution, stabilization, or until it is determined that study participation is not the cause. If a participant is seen in the ER and within seven days is admitted to the hospital for a procedure related to that ER visit, a separate SAE does not need to be completed. The original SAE for the ER visit should be edited to reflect the ER visit and the hospitalization.

Drs. Zhang and Vongpatanasin will be responsible for timely reporting to the NIH and the SO and provide reports of SAEs for review by the SO either by e-mail or at their meetings.

The expedited report will be followed by a detailed, written SAE report as soon as possible. Follow up information may be required and asked directly by the SO, or NIA Program Officer or his/her representative.

6.4 Data and Safety Monitoring Plan (DSMP)

According to the NIH guidelines, the Safety Officer is an independent individual who performs data and safety monitoring activities in low-risk, single site clinical studies. The Safety Officer advises the NIH Program Director and Principal Investigator (PI) regarding participant safety, scientific integrity and ethical conduct of a study. The Principal Investigator typically proposes an independent Safety Officer, usually a physician, with relevant study and disease specific expertise, and submits the individual's name for review and approval by the NIH Program Officer.

Safety Officer (SO) will receive the manual of operating procedures, which typically contains the study protocol and safety monitoring plan, before study enrollment begins.

To remain objective, SO will maintain independence from the study. Accordingly, SO will not be directly involved in the conduct of the study and should not have scientific, proprietary, financial or other interests that may affect independent decision-making.

At predetermined intervals, the study statistician will prepare adverse event reports to be reviewed by SO. The adverse events are reported in aggregate as requested. Serious adverse events are generally reported as they occur. The safety monitoring plan should specify how data are to be presented. In addition, the safety monitoring plan should specify the process for reporting safety concerns among the Institutional Review Board, the Safety Officer and the NIH Program Officer.

SO will provide independent safety monitoring in a timely fashion to assure patient safety and study quality.

At the beginning of the trial, SO will review the manual of operating procedures, containing the study protocol, study forms, and safety monitoring plan, for scope and comprehensiveness. The monitoring plan should delineate data preparation functions, the review process, and the role of the Safety Officer. The monitoring plan also specifies the contents and format of the reports, their frequency, and triggers for ad hoc reviews. Stopping rules, if appropriate, should outline the conditions under which a study may be stopped prematurely. The Safety Officer may suggest modifications to the protocol, the monitoring plan and the reports that will routinely be prepared by the study statistician.

The primary focus of the Safety Officer's monitoring activity is participant safety. The Safety Officer reviews adverse event reports prepared by the study statistician.

Serious adverse events are generally reviewed as they occur. The Safety Officer will notify the NIA if a pattern of events occurs and will suggest prevention measures.

For unexpected and/or related serious adverse events, SO will contact the NIH Program representative. In addition, the Safety Officer may request individual patient records, including laboratory data, clinical records, and other study related data, to evaluate these events against the known safety profile of the study treatment and the disease. The Safety Officer may recommend actions including partial or complete unblinding, and/or modifying or terminating the study.

In addition to safety monitoring, the Safety Officer may review enrollment data, demographic information, retention status, and other reports prepared by the study statistician that describe study performance and progress. SO will provide a report to NIH that describes study safety, progress and performance and provides recommendations regarding safe continuation or early termination of the trial.

The monitoring plan may require SO to evaluate the general performance of the study, including periodic assessment of participant recruitment, accrual and retention, protocol adherence, and data quality and timeliness. SO may also review any interim analyses to ensure that once the objectives of the study are met, outcome differences are detected or stopping rule thresholds are reached, the study will conclude.

Confidentiality must be maintained throughout all phases of the trial, including monitoring, preparation of interim results, review, and response to monitoring recommendations. Thus, SO will not receive patient identifiers, will maintain study confidentiality and will not share data.

After review and evaluation of the specified periodic reports prepared by the statistician, SO will prepare a summary cover letter for submission to the NIA. The letter provides comments on the report, discusses any concerns or suggestions for change, and recommends to NIA continuation or cessation of the trial.

Section7. Sample Size and Statistical Methods

Aim 1: **Determine the effects of hypertension on intracranial pulsatility, CSF Aβ and tau, white matter integrity and neural network functional connectivity**. Hypotheses: Hypertension is associated with: **1)** augmented central pulsatility, but reduced intracranial pulsatility; **2)** reductions in CSF soluble $A\beta_{42}$, but increases in phosphorylated tau and total tau; **3)** disruptions in brain white matter integrity and functional connectivity.

Rationale and anticipated results We anticipate that central pulsatility is increased, while intracranial pulsatility is reduced in patients with hypertension, which are associated with increases in cerebrovascular impedance and/or reductions in brain tissue compliance.[47, 48] We anticipate that CSF $A\beta_{42}$ is reduced, but total tau and phosphorylated tau are increased in hypertension, suggesting impact of intracranial pulsatility on brain Aβ and tau homeostasis via reductions in glymphatic Aβ and tau clearance.[9, 10] We expect that brain white matter integrity in the regions related to the episodic memory and executive function is reduced in hypertension, which is associated with reductions in DMN and FPN connectivity. We focus on a neural network approach to assess the impact of hypertension on brain structure and function because it is likely to detect early brain changes.[16, 18, 22, 36] Gray matter atrophy, white matter lesions, and executive dysfunction are observed in older adults with hypertension, and are likely influenced by age and severity of hypertension.[15] We do not propose to use PET amyloid imaging to assess brain Aβ burden because it is expensive, and only measures the amount of aggregated fibrillary

Aβ in the cerebral cortex (extracellular plaques), which manifested only in about one-third of cognitively normal older adults.[5, 49] Conversely, CSF soluble Aβ and tau are reliable biomarkers of brain aging and AD, and reflect a steady-state homeostasis (or a metabolic equilibrium) between the production and clearance of brain Aβ and tau which may change in response to modifiable risk factors such as lowering BP, thus suitable for the purpose of this project.[50, 51]

Statistical analysis and sample size justification Descriptive analysis will be performed where we summarize continuous variables by mean and standard deviation, and categorical variables by counts and percentages. Appropriate transformation will be performed when necessary so that the normality assumption is not violated. Comparisons between groups will be performed using two-sample T test or Chi-square test. The nonparametric Wilcoxon–Mann–Whitney test and Fisher's exact test will be employed when necessary. We report statistical significance for a p-value of <0.05 for the primary outcome measure of group differences in the magnitude of intracranial pulsatility. Due to the exploratory nature of the proposed study, no adjustments for multiple comparisons are planned a priori for other outcome measures. Adjustments for multiple comparisons for neuroimaging data analysis will be performed using the established methods.[36, 37] As a secondary data analysis, we propose to conduct mediation analysis to assess whether the effects of hypertension on brain Aβ and tau, neural network structure and function are mediated by alterations in intracranial pulsatility. Specifically, to establish that the effect of X (differences in BP) on the outcome Y (e.g., brain neural network structure or function) is mediated by M (intracranial pulsatility), the following four steps need to be satisfied: 1) The effect of X on Y must be significant; 2) The effect of X on M much be significant; 3) The effect of M on Y controlling for X must be significant; 4) the effect of X on Y adjusted for M should be smaller than that observed in the step 1. We will use linear models, and the difference-in-coefficients tests will be performed.[52] Sample size and power analysis are based on group differences in the magnitude of intracranial pulsatility, that is, measurements of pulsatile oscillations in brain tissue volume and regional brain tissue movements (local pixel displacement). Previous studies and our pilot data indicate that the magnitude of pulsatile oscillations in total brain tissue volume during a cardiac cycle is about 0.80 ± 0.15 ml, while the local brain tissue movement at the edge of the lateral ventricle is about 0.165 ± 0.042 mm in all three spatial directions.[38, 43, 44] With a total of 120 subjects (40 normotensive and 80 hypertensive), a two-sample T test can detect a mean difference of 0.083 ml of changes in brain tissue volume between the two groups with 80% power and 5% two-sided type I error. In addition, a mean difference of 0.023 mm of local brain tissue movement can be detected between the two groups with 80% power and 5% two-sided type I error.[53] All statistical analysis will be performed using SAS 9.3 (SAS Institute, Cary, NC).

Potential problems We do not anticipant major problems in the proposed MRI and TCD studies because the proposed procedures have been used in our previous studies.[35-37, 45] However, the magnitudes of pulsatile oscillations in brain tissue movement and CSF in a cardiac cycle are relatively small (Fig 3), thus robust velocity post-processing procedures are essential to improve the accuracy and reliability of these measurements. The procedures for velocity post-processing have been developed by Dr. Zhu (Co-PI of this project) and their accuracy and reliability are demonstrated in previous studies.[38, 54, 55] Essentially, to reduce the possibility of a spatially dependent offset velocity due to eddy currents or head motion, the velocity at each pixel location will be corrected by subtraction of the time-average "velocity" of a nearby solid brain tissue "background" within a 29 mm × 29 mm region having the interested pixel at its center.[38, 44, 56] In calculation of the velocity of the brain tissue, the velocity at each pixel location will be corrected by a subtraction of the time-average "velocity" of the pixel itself obtained over a full cardiac cycle. This approach is based on the fact that brain tissue is unlikely to accumulate a net displacement over a cardiac cycle.[38, 44, 56] The CINE PC-MRI also assumes that blood flow, CSF flow and brain motion patterns remain relatively constant and are in sync with the cardiac cycle. Following this assumption, we will collect PC-MRI data at the second half of the scan session after the subjects are accustomed to the MRI environment and relaxing music will be provided to reduce potential discomfort. rs-fMRI connectivity may be influenced by the data pre-processing methods to remove vascular contamination that is not related to neuronal activity.[37, 57] The most controversial debate on the pre-processing steps is the global signal removal strategy.[57] Our team is actively working on a better understanding of the impact of global signal removal on fMRI connectivity, and has developed more un-biased noise-removal techniques.[37] rs-fMRI reproducibility is also important to quantify the within-subject modification of the DMN and FPN. To improve the reproducibility, we propose to collect a relatively long but still durable 12-minutes of rs-fMRI dataset. We have considered that CSF samples may not be obtained from all study participants. We plan to use an education video as well as other materials provided by the Alzheimer's Disease Cooperative Study to improve participant's understanding of LP procedures and to increase enrollment. Based on our own experience and other trials, CSF samples are likely to be obtained from about 50-60% of study participants.[32, 58] We will use consent to LP as an inclusion criteria if the enrollment target is below the expected values when we have about 50% of participants being enrolled in the project. Finally, we acknowledge that we cannot measure directly brain Aβ and tau clearance through the glymphatic system. CSF soluble Aβ and tau reflect a steady-state homeostasis between the production and clearance of Aβ and tau which ultimately influences brain aging and AD.[2, 50] Thus, an association between intracranial pulsatility and CSF Aβ and tau only suggest, but cannot prove a causal

relationship. Despite these limits, findings from this project will provide significant new insights into the effects of hypertension and antihypertensive treatment on intracranial pulsatility, AD biomarkers, brain neural network structure and function.

Aim 2: Determine the effects of antihypertensive treatments on intracranial pulsatility, CSF Aβ and tau, brain white matter integrity and neural network functional connectivity. Hypotheses: compared to standard care, intensive treatment confers more benefits by: **1)** reductions in central pulsatility, but increases intracranial pulsatility; **2)** increases in CSF $A\beta_{42}$, but reductions in phosphorylated tau and total tau; **3)** improvement in brain white matter integrity and functional connectivity.

Rationale and anticipated results The primary outcome measures of Aim 2 are BP treatment induced changes in intracranial pulsatility, CSF Aβ and tau. We anticipate that cerebrovascular resistance/impedance is reduced, and brain tissue compliance is improved after BP lowering, and these changes in turn increase global as well as regional intracranial pulsatility.[47, 48] We anticipate antihypertensive treatment alters central and/or intracranial pulsatility as well as the dynamic relationships between them. An important strength of this project is that we will be able to assess whether and to what extent each of the systemic and cerebrovascular factors contribute to the changes in intracranial pulsatility. Recent studies including our own work have demonstrated that increases in SBP and PBP are associated with increases in brain Aβ burden and elevated CSF tau in older adults, suggesting a potential link between hypertension and AD pathology.[4, 5, 49] We anticipate that compared to the baseline, CSF $A\beta_{42}$ level will be higher, and total and phosphorylated tau level will be lower after antihypertensive treatment, and that larger changes are conferred by intensive BP lowering when compared to the standard care.[50] We will determine whether changes in CSF $A\beta_{42}$ and tau are associated with changes in intracranial pulsatility, suggesting improvement in brain Aβ and tau clearance through the glymphatic system.[8, 12] Furthermore, we anticipant that brain white matter integrity in the regions related to the episodic memory and executive function, DMN and FPN functional connectivity is improved after intensive BP treatment and that these improvements are associated with improvement in global and domain specific neurocognitive function. We expect that the effects of BP treatment on brain white matter integrity, neural network structure and function are related to the magnitude of BP lowering. We have considered that although the presence of intracranial pulsatility is critical for brain Aβ and tau clearance,[10, 59] changes in intracranial pulsatility may have direct effects on brain perfusion and brain neural network structure and function through either Aβ and tau dependent or independent mechanisms.[3, 15, 60, 61] We will measure regional brain perfusion using ASL and conduct multivariable

linear regression and mediation analysis to determine whether changes in intracranial pulsatility are related to changes in brain white matter integrity and functional connectivity after adjusting for their effects on CSF Aβ and tau concentration.

Statistical analysis and sample size justification Based on the measurements at baseline, 6 months, and 12 months, we will construct linear mixed models to detect the differences in the rate of changes of outcome measures between the intensive treatment and the standard care group. The models include subject random effects to account for the correlations among the measurements. The generalized estimation equation (GEE) approach will be employed to make inference about the models.[53] In addition, we will conduct mediation analysis to assess whether the effects of BP lowering on CSF Aβ and tau concentrations, white matter microstructural integrity and neural network functional connectivity are mediated by changes in intracranial pulsatility. The causal-steps approach will be employed for the mediation analysis,[62] and linear models and the difference-in-coefficients tests will be performed.[52] We will build multivariate regression models to assess the association between the magnitude of BP reductions and changes in intracranial pulsatility. The outcome and predictor variables will be the within-subject changes in intracranial pulsatility and BP at one year from the baseline, respectively. The regression model will control for other confounding variables including intervention, age, sex, BP medication and central arterial stiffness. The final model will be determined based on step-wise variable selection as well as clinical considerations. Sample size for the comparison of the slope of the magnitude of pulsatile oscillations in brain tissue volume or regional brain tissue movement between the treatment groups: We conducted power analysis based on the GEE sample size approach developed for the test of slopes using longitudinal measurements.[63, 64] Based on a previous study, we assume an equal standard deviation of 0.15 ml for the two groups.[43] At a 5% two-sided type I error and 80% power, by enrolling 40 patients in each group, we can detect a difference of 0.11 ml/year in the slope between the two groups. This calculation assumes a compound symmetric correlation structure, a moderate within-subject correlation of 0.25, and a dropout rate of 10% over the 1 year study period. We have also assessed the impact of within-subject correlation on power analysis. For example, when the within-subject correlation changes from 0.1 to 0.5, the difference in the slopes that can be detected ranges from 0.1 to 0.13 ml/year. Sample size for the comparison of changes in CSF at one year from baseline between the treatment groups: Assuming that a minimum of 50% of patients (that is, 20 patients from each group) will contribute to both baseline and 12-month measurements. A previous ADNI study in normal older adults suggests that the standard deviation of annualized change in CSF $A\beta_{42}$ is ~ 0.84 pg/ml.[58] With 20 patients from each group, using a two-sample T test, we can detect a change of 0.67 pg/ml of CSF $A\beta_{42}$

between the two treatment groups with a power of 80% and a one-sided type I error of 5%. Sample size for the comparison of brain white matter integrity and neural network functional connectivity: we will compare changes in DTI metrics to assess brain white matter integrity at 1 year from the baseline between the treatment groups, assuming a dropout rate of 10% from each group. A previous study in middle-aged and older adults suggests that the standard deviation of annualized change in global fractional anisotropy (FA) based on TBSS analysis is about 0.003.[65] With 36 patients from each group, using a two-sample T test, we can detect a change of 0.002 of FA in the intensive treatment group compared with the standard care group with a power of 80% and a two-sided type I error of 5%. Similarly, assuming the standard deviation of annualized change in the global DMN functional connectivity is about 0.11 using a two-sample T test,[66] we can detect a change of 0.074 of functional connectivity between the two groups with a power of 80% and a two-sided type I error of 5%.

Section8. Risk/Benefit Assessment

To the study subjects: Occasionally, an unknown condition that might require medical attention (such as a brain tumor, hypertension and diabetes) could be discovered during a careful history and physical exam, and with MRI scan. In addition, being followed clinically by the study physician and nurse practitioner, and participating in the proposed intervention of intensive reduction of blood pressure are likely to be beneficial for the participants to improve cardiovascular and brain health.

To others with similar problems: This project will study the impact of hypertension and intensive antihypertensive treatment on brain structure and function. The new knowledge obtained will provide mechanistic understanding of effects of hypertension and antihypertensive treatments on brain health in older adults.

To society in general More than 60% of older adults age ≥ 60 have hypertension which is an important risk factor for age-related cognitive decline and Alzheimer's disease. Understanding of the underlying mechanisms by which hypertension leads to brain damage and potential benefits of antihypertensive treatments on brain structure and function is fundamentally important for developing effective interventions to prevent age-related cognitive decline and dementia - one of the significant challenges we are facing with the aging population. The relatively minor risks, associated with the potential benefits to the individuals and society in general reflect a favorable risk/benefit ratio.

8.1 IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

We are facing one of the most significant challenges of the 21st century in how to maintain brain health in older adults. A mechanistic understanding of the role of biomechanical forces (i.e., central and intracranial pulsatility) in brain Aβ and tau protein homeostasis in older adults with hypertension is potentially important for developing novel biomarkers and effective interventions to prevent or slow age-related cognitive decline and dementia.

References

1. Mawuenyega KG, Sigurdson W, Ovod V, Munsell L, Kasten T, Morris JC, Yarasheski KE and Bateman RJ. Decreased clearance of CNS beta-amyloid in Alzheimer's disease. *Science*. 2010;330:1774.

2. Roberts KF, Elbert DL, Kasten TP, Patterson BW, Sigurdson WC, Connors RE, Ovod V, Munsell LY, Mawuenyega KG, Miller-Thomas MM, Moran CJ, Cross DT, 3rd, Derdeyn CP and Bateman RJ. Amyloid-beta efflux from the central nervous system into the plasma. *Ann Neurol*. 2014;76:837-44.

3. Hughes TM, Craft S and Lopez OL. Review of 'the potential role of arterial stiffness in the pathogenesis of Alzheimer's disease'. *Neurodegenerative disease management*. 2015;5:121-35.

4. Nation DA, Edmonds EC, Bangen KJ, Delano-Wood L, Scanlon BK, Han SD, Edland SD, Salmon DP, Galasko DR, Bondi MW and Alzheimer's Disease Neuroimaging Initiative I. Pulse pressure in relation to tau-mediated neurodegeneration, cerebral amyloidosis, and progression to dementia in very old adults. *JAMA Neurol*. 2015;72:546-53.

5. Rodrigue KM, Rieck JR, Kennedy KM, Devous MD, Sr., Diaz-Arrastia R and Park DC. Risk factors for beta-amyloid deposition in healthy aging: vascular and genetic effects. *JAMA Neurol*. 2013;70:600-6.

6. Crary JF, Trojanowski JQ, Schneider JA, Abisambra JF, Abner EL, Alafuzoff I, Arnold SE, Attems J, Beach TG, Bigio EH, Cairns NJ, Dickson DW, Gearing M, Grinberg LT, Hof PR, Hyman BT, Jellinger K, Jicha GA, Kovacs GG, Knopman DS, Kofler J, Kukull WA, Mackenzie IR, Masliah E, McKee A, Montine TJ, Murray ME, Neltner JH, Santa-Maria I, Seeley WW, Serrano-Pozo A, Shelanski ML, Stein T, Takao M, Thal DR, Toledo JB, Troncoso JC, Vonsattel JP, White CL, 3rd, Wisniewski T, Woltjer RL, Yamada M and Nelson PT. Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta neuropathologica*. 2014;128:755-66.

7. Saido T and Leissring MA. Proteolytic degradation of amyloid beta-protein. *Cold Spring Harb Perspect Med*. 2012;2:a006379.

8. Carare RO, Hawkes CA, Jeffrey M, Kalaria RN and Weller RO. Review: cerebral amyloid angiopathy, prion angiopathy, CADASIL and the spectrum of protein elimination failure angiopathies (PEFA) in neurodegenerative disease with a focus on therapy. *Neuropathol Appl Neurobiol*. 2013;39:593-611.

9. Iliff JJ, Lee H, Yu M, Feng T, Logan J, Nedergaard M and Benveniste H. Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. *J Clin Invest*. 2013;123:1299-309.

10. Nedergaard M. Neuroscience. Garbage truck of the brain. *Science*. 2013;340:1529-30.

11. Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, Derecki NC, Castle D, Mandell JW, Lee KS, Harris TH and Kipnis J. Structural and functional features of central nervous system lymphatic vessels. *Nature*. 2015;523:337-41.

12. Iliff JJ, Wang M, Zeppenfeld DM, Venkataraman A, Plog BA, Liao Y, Deane R and Nedergaard M. Cerebral arterial pulsation drives paravascular CSF-interstitial fluid exchange in the murine brain. *J Neurosci*. 2013;33:18190-9.

13. Iadecola C, Park L and Capone C. Threats to the mind: aging, amyloid, and hypertension. *Stroke*. 2009;40:S40-4.

14. Soros P, Whitehead S, Spence JD and Hachinski V. Antihypertensive treatment can prevent stroke and cognitive decline. *Nature reviews*. 2013;9:174-8.

15. Tzourio C, Laurent S and Debette S. Is hypertension associated with an accelerated aging of the brain? *Hypertension*. 2014;63:894-903.

16. Maillard P, Seshadri S, Beiser A, Himali JJ, Au R, Fletcher E, Carmichael O, Wolf PA and DeCarli C. Effects of systolic blood pressure on white-matter integrity in young adults in the Framingham Heart Study: a cross-sectional study. *Lancet Neurol*. 2012;11:1039-47.

17. Rosano C, Abebe KZ, Aizenstein HJ, Boudreau R, Jennings JR, Venkatraman V, Harris TB, Yaffe K, Satterfield S, Newman AB and Health ABCS. Longitudinal systolic blood pressure characteristics and integrity of white matter tracts in a cohort of very old black and white adults. *Am J Hypertens*. 2015;28:326-34.

18. Li X, Liang Y, Chen Y, Zhang J, Wei D, Chen K, Shu N, Reiman EM and Zhang Z. Disrupted Frontoparietal Network Mediates White Matter Structure Dysfunction Associated with Cognitive Decline in Hypertension Patients. *J Neurosci*. 2015;35:10015-24.

19. Pievani M, Filippini N, van den Heuvel MP, Cappa SF and Frisoni GB. Brain connectivity in neurodegenerative diseases--from phenotype to proteinopathy. *Nature reviews*. 2014;10:620-33.

20. Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, Roffman JL, Smoller JW, Zollei L, Polimeni JR, Fischl B, Liu H and Buckner RL. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol*. 2011;106:1125-65.

21. Weintraub S, Dikmen SS, Heaton RK, Tulsky DS, Zelazo PD, Bauer PJ, Carlozzi NE, Slotkin J, Blitz D, Wallner-Allen K, Fox NA, Beaumont JL, Mungas D, Nowinski CJ, Richler J, Deocampo JA, Anderson JE, Manly JJ, Borosh B, Havlik R, Conway K, Edwards E, Freund L, King JW, Moy C, Witt E and Gershon RC. Cognition assessment using the NIH Toolbox. *Neurology*. 2013;80:S54-64.

22. Iadecola C, Yaffe K, Biller J, Bratzke LC, Faraci FM, Gorelick PB, Gulati M, Kamel H, Knopman DS, Launer LJ, Saczynski JS, Seshadri S, Zeki Al Hazzouri A, American Heart Association Council on H, Council on Clinical C, Council on Cardiovascular Disease in the Y, Council on C, Stroke N, Council on Quality of C, Outcomes R and Stroke C. Impact of Hypertension on Cognitive Function: A Scientific Statement From the American Heart Association. *Hypertension*. 2016;68:e67-e94.

23. Dufouil C, Chalmers J, Coskun O, Besancon V, Bousser MG, Guillon P, MacMahon S, Mazoyer B, Neal B, Woodward M, Tzourio-Mazoyer N and Tzourio C. Effects of blood pressure lowering on cerebral white matter hyperintensities in patients with stroke: the PROGRESS

(Perindopril Protection Against Recurrent Stroke Study) Magnetic Resonance Imaging Substudy. *Circulation*. 2005;112:1644-50.

24. Godin O, Tzourio C, Maillard P, Mazoyer B and Dufouil C. Antihypertensive treatment and change in blood pressure are associated with the progression of white matter lesion volumes: the Three-City (3C)-Dijon Magnetic Resonance Imaging Study. *Circulation*. 2011;123:266-73.

25. White WB, Marfatia R, Schmidt J, Wakefield DB, Kaplan RF, Bohannon RW, Hall CB, Guttmann CR, Moscufo N, Fellows D and Wolfson L. INtensive versus standard ambulatory blood pressure lowering to prevent functional DeclINe in the ElderlY (INFINITY). *Am Heart J*. 2013;165:258-265 e1.

26. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, Lackland DT, LeFevre ML, MacKenzie TD, Ogedegbe O, Smith SC, Jr., Svetkey LP, Taler SJ, Townsend RR, Wright JT, Jr., Narva AS and Ortiz E. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *Jama*. 2014;311:507-20.

27. White WB, Wolfson L, Wakefield DB, Hall CB, Campbell P, Moscufo N, Schmidt J, Kaplan RF, Pearlson G and Guttmann CR. Average daily blood pressure, not office blood pressure, is associated with progression of cerebrovascular disease and cognitive decline in older people. *Circulation*. 2011;124:2312-9.

28. Zhang R, Vongpatanasin W and Levine BD. Faster brain shrinkage in the ACCORD MIND study – an unexpected result? *JAMA Internal Medicine* 2014;In press.

29. Folstein MF, Folstein SE and McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-98.

30. Donohue MC, Sperling RA, Salmon DP, Rentz DM, Raman R, Thomas RG, Weiner M, Aisen PS, Australian Imaging B, Lifestyle Flagship Study of A, Alzheimer's Disease Neuroimaging I and Alzheimer's Disease Cooperative S. The preclinical Alzheimer cognitive composite: measuring amyloid-related decline. *JAMA Neurol*. 2014;71:961-70.

31. New Frontier: Developing Outcome Measures for Pre-dementia Trials. *Alzheimer's Association* 2013; http://www.alzforum.org/webinars/new-frontier-developing-outcome-measures-pre-dementia-trials.

32. Monson NL, Ireland SJ, Ligocki AJ, Chen D, Rounds WH, Li M, Huebinger RM, Munro Cullum C, Greenberg BM, Stowe AM and Zhang R. Elevated CNS inflammation in patients with preclinical Alzheimer's disease. *J Cereb Blood Flow Metab*. 2014;34:30-3.

33. Saxby BK, Harrington F, Wesnes KA, McKeith IG and Ford GA. Candesartan and cognitive decline in older patients with hypertension: a substudy of the SCOPE trial. *Neurology*. 2008;70:1858-66.

34. Cutter GR, Baier ML, Rudick RA, Cookfair DL, Fischer JS, Petkau J, Syndulko K, Weinshenker BG, Antel JP, Confavreux C, Ellison GW, Lublin F, Miller AE, Rao SM, Reingold S, Thompson A and Willoughby E. Development of a multiple sclerosis functional composite as a clinical trial outcome measure. *Brain*. 1999;122 (Pt 5):871-82.

35. Tarumi T, Ayaz Khan M, Liu J, Tseng BY, Parker R, Riley J, Tinajero C and Zhang R. Cerebral hemodynamics in normal aging: central artery stiffness, wave reflection, and pressure pulsatility. *J Cereb Blood Flow Metab*. 2014;34:971-8.

36. Tarumi T, de Jong DL, Zhu DC, Tseng BY, Liu J, Hill C, Riley J, Womack KB, Kerwin DR, Lu H, Munro Cullum C and Zhang R. Central artery stiffness, baroreflex sensitivity, and brain white matter neuronal fiber integrity in older adults. *Neuroimage*. 2015;110:162-70.

37. Zhu DC, Tarumi T, Khan MA and Zhang R. Vascular coupling in resting-state fMRI: evidence from multiple modalities. *J Cereb Blood Flow Metab*. 2015.

38. Zhu DC, Xenos M, Linninger AA and Penn RD. Dynamics of lateral ventricle and cerebrospinal fluid in normal and hydrocephalic brains. *J Magn Reson Imaging*. 2006;24:756-70.

39. Liu P, Xu F and Lu H. Test-retest reproducibility of a rapid method to measure brain oxygen metabolism. *Magn Reson Med*. 2013;69:675-81.

40. Luetmer PH, Huston J, Friedman JA, Dixon GR, Petersen RC, Jack CR, McClelland RL and Ebersold MJ. Measurement of cerebrospinal fluid flow at the cerebral aqueduct by use of phase-contrast magnetic resonance imaging: technique validation and utility in diagnosing idiopathic normal pressure hydrocephalus. *Neurosurgery*. 2002;50:534-43; discussion 543-4.

41. Veenith TV, Carter E, Grossac J, Newcombe VF, Outtrim JG, Lupson V, Williams GB, Menon DK and Coles JP. Inter subject variability and reproducibility of diffusion tensor imaging within and between different imaging sessions. *PloS one*. 2013;8:e65941.

42. Huang L, Wang X, Baliki MN, Wang L, Apkarian AV and Parrish TB. Reproducibility of structural, resting-state BOLD and DTI data between identical scanners. *PloS one*. 2012;7:e47684.

43. Alperin NJ, Lee SH, Loth F, Raksin PB and Lichtor T. MR-Intracranial pressure (ICP): a method to measure intracranial elastance and pressure noninvasively by means of MR imaging: baboon and human study. *Radiology*. 2000;217:877-85.

44. Enzmann DR and Pelc NJ. Brain motion: measurement with phase-contrast MR imaging. *Radiology*. 1992;185:653-60.

45. Zhu YS, Tseng BY, Shibata S, Levine BD and Zhang R. Increases in cerebrovascular impedance in older adults. *J Appl Physiol*. 2011;111:376-81.

46. Liu J, Zhu YS, Khan MA, Brunk E, Martin-Cook K, Weiner MF, Cullum CM, Lu H, Levine BD, Diaz-Arrastia R and Zhang R. Global brain hypoperfusion and oxygenation in amnestic mild cognitive impairment. *Alzheimers Dement*. 2014;10:162-70.

47. Lipsitz LA, Gagnon M, Vyas M, Iloputaife I, Kiely DK, Sorond F, Serrador J, Cheng DM, Babikian V and Cupples LA. Antihypertensive therapy increases cerebral blood flow and carotid distensibility in hypertensive elderly subjects. *Hypertension*. 2005;45:216-21.

48. Zhang R, Witkowski S, Fu Q, Claassen JA and Levine BD. Cerebral hemodynamics after short- and long-term reduction in blood pressure in mild and moderate hypertension. *Hypertension*. 2007;49:1149-55.

49. Tarumi T, Harris T, Hill C, German Z, Riley J, Turner M, Womack KB, Kerwin DR, Monson NL, Stowe AM, Mathews D, Cullum CM and Zhang R. Amyloid Burden and Sleep Blood Pressure in Amnestic 1 Mild Cognitive Impairment. *Neurology*. 2015;In press.

50. Blennow K, Hampel H, Weiner M and Zetterberg H. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. *Nature reviews*. 2010;6:131-44.

51. Ooms S, Overeem S, Besse K, Rikkert MO, Verbeek M and Claassen JA. Effect of 1 night of total sleep deprivation on cerebrospinal fluid beta-amyloid 42 in healthy middle-aged men: a randomized clinical trial. *JAMA Neurol*. 2014;71:971-7.

52. Mackinnon DP, Warsi G and Dwyer JH. A Simulation Study of Mediated Effect Measures. *Multivariate behavioral research*. 1995;30:41.

53. Liang KY and Zeger SL. Longitudinal data analysis using generalized linear models *Biometrika*. 1986;73.

54. Linninger AA, Xenos M, Zhu DC, Somayaji MR, Kondapalli S and Penn RD. Cerebrospinal fluid flow in the normal and hydrocephalic human brain. *IEEE Trans Biomed Eng*. 2007;54:291-302.

55. Tangen KM, Hsu Y, Zhu DC and Linninger AA. CNS wide simulation of flow resistance and drug transport due to spinal microanatomy. *J Biomech*. 2015;48:2144-54.

56. Poncelet BP, Wedeen VJ, Weisskoff RM and Cohen MS. Brain parenchyma motion: measurement with cine echo-planar MR imaging. *Radiology*. 1992;185:645-51.

57. Murphy K, Birn RM, Handwerker DA, Jones TB and Bandettini PA. The impact of global signal regression on resting state correlations: are anti-correlated networks introduced? *Neuroimage*. 2009;44:893-905.

58. Lo RY, Hubbard AE, Shaw LM, Trojanowski JQ, Petersen RC, Aisen PS, Weiner MW and Jagust WJ. Longitudinal change of biomarkers in cognitive decline. *Arch Neurol*. 2011;68:1257-66.

59. Iliff JJ, Chen MJ, Plog BA, Zeppenfeld DM, Soltero M, Yang L, Singh I, Deane R and Nedergaard M. Impairment of glymphatic pathway function promotes tau pathology after traumatic brain injury. *J Neurosci*. 2014;34:16180-93.

60. Mitchell GF, van Buchem MA, Sigurdsson S, Gotal JD, Jonsdottir MK, Kjartansson O, Garcia M, Aspelund T, Harris TB, Gudnason V and Launer LJ. Arterial stiffness, pressure and flow pulsatility and brain structure and function: the Age, Gene/Environment Susceptibility--Reykjavik study. *Brain*. 2011;134:3398-407.

61. O'Rourke MF and Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. *Hypertension*. 2005;46:200-4.

62. Judd C and Kenny DA. *Estimating the effects of social interventions.* Cambridge, England: Cambridge University Press; 1981.

63. Jung SH and Ahn C. Sample size estimation for GEE method for comparing slopes in repeated measurements data. *Statistics in medicine*. 2003;22:1305-15.

64. Zhang S and Ahn C. Effects of correlation and missing data on sample size estimation in longitudinal clinical trials. *Pharmaceutical statistics*. 2010;9:2-9.

65. Sexton CE, Walhovd KB, Storsve AB, Tamnes CK, Westlye LT, Johansen-Berg H and Fjell AM. Accelerated changes in white matter microstructure during aging: a longitudinal diffusion tensor imaging study. *J Neurosci*. 2014;34:15425-36.

66. Zhu DC, Covassin T, Nogle S, Doyle S, Russell D, Pearson RL, Monroe J, Liszewski CM, DeMarco JK and Kaufman DI. A potential biomarker in sports-related concussion: brain functional connectivity alteration of the default-mode network measured with longitudinal resting-state fMRI over thirty days. *J Neurotrauma*. 2015;32:327-41.

Table1. Screening, Baseline and Follow-up Schedule Events for All Study Arms

Procedures	**Phone-Screening**	**In-person Screening**	**Baseline (3 visits)**			**Day 0**	**Intervention**							**Close out (12 Month)**		
Visit ID	***PS***	***SV1***	***BL1***	***BL2***	***BL3***	***Day0***	***wk2***	***wk 4***	***wk6***	***wk8***	***M3***	***M6***	***M9***	***FU1***	***FU2***	***FU3***
Visit Windows			*± 2 wks*	*± 2 wks*	*± 2 wks*	*Day 0 ± 2 wks*	*± 2 wks*			*± 2 wks*			*± 2 wks*	*± 1 wks*	*± 1 wks*	*± 1 wks*
Estimated Hours	*30mins*	*5hr*	*2.5hrs*	*3.5hrs*	*1.5hrs*	*2hrs*	*4hrs*	*2hrs*	*2hrs*	*2hrs*	*4hrs*	*4hrs*	*4hrs*	*5hrs*	*3.5hrs*	*1.5 hrs*
Phone Screen Questionnaire/Eligibility	X															
Informed consent/ HIPAA		X														
Inclusion/Exclusion Criteria Review		X														
Seated/Standing Clinic BP		X					X	X	X	X	X	X	X	X		
24-h Ambulatory BP*		X					X	X	X	X	X	X		X		
MMSE		X														
Height/ Weight /BMI		X					X			X			X	X		
Subject Demographics		X														
Subject Family History		X														
Subject Medications		X					X			X			X	X	X	
Subject Health History		X												X		
Physical/Neurological Exam		X								X				X		
ECG		X												X		
Neurocognitive function (NIH-TB)/NIH PROMIS			X									X			X	
Phosphorous and Magnesium				X												
Basic Metabolic Panel (BMP) †				X			X	X	X	X	X		X			
Complete Metabolic Panel (CMP), Hgb A1C, Hematocrit		X														

Complete Metabolic Panel (CMP), HgbA1C										X				X		
24 Hour Urine Collection				x												
Plasma, serum and whole blood long-term storage (Fasting), Lipid Panel (Fasting)				X										X		
MRI					X											X
TCD Autoregulation/Vascular function			X									X				X
Randomization						X										
Intervention Orientation						X										
BP Medication Titration							X	X	X	X	X	X	X			
Treatment Medication Compliance							X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment							X	X	X	X	X	X	X	X	X	X
* 24-h ABP will be performed during week 2-10 when clinic BP reaches goal, and during wk 12 or M3 (unless 24-h ABP already reaches goal between wk 2-10), M6, and 12																
† BMP will be performed at wk 2, and prn only when diuretics, ACEI, or ARB are added to regimen or the doses of these drugs are increased.																
** LP will be performed only in subjects who agree to this part of the study																
Baseline Visit Procedures can be done at different order with some restrictions: MRI cannot be fasting, must give snacks prior to MRI if paired with fasting blood draw																