1.a. **Full Title**: Preventing dementia: The case of elevated blood pressure in older persons - What to treat with?

b. **Abbreviated Title (Length 26 characters)**: BP, cognitive decline & dementia

2. **Writing Group**: Writing group members: Lenore Launer, Caroline Phillips, Jie Ding, Rebecca Gottesman, B. Gwen Windham, Michael Griswold, Cornelia Van Duijn, Arfan Ikram, Sanaz Sedaghat Harabarjan, Christophe Tzourio, Stéphanie Debette, Sudha Seshadri, Matthew Pase, Jayandra J. Himali, and Alexander, V. Sergienko, Thomas H. Mosley

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. ___LL___ [please confirm with your initials electronically or in writing]

**First author**: Lenore Launer, PhD

Address: Intramural Research Program, National Institute on Aging, 7201 Wisconsin Avenue, Suite 3c-309, Bethesda, MD, 20814

Phone: +1-301-496-1178

Fax: +1-301-496-4006

E-mail: LaunerL@nia.nih.gov

**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

Name: B. Gwen Windham MD MHS

Address: 2500 N. State St; Jackson, MS 39216

Phone: 601-984-5645

E-mail: gwindham@umc.edu

3. **Timeline**: 12 months to submission of manuscript

4. **Rationale**: As a part of recommending BP control in older persons, treatment choices have to be considered. There are five major classes of anti-hypertensive medications, with different mechanisms of action that may be relevant for cerebral health. For example, calcium channel blockers that cross the blood-brain barrier target the oxidative stress and toxic influx of calcium in the brain; the renin angiotensin system inhibitors (ACEI) may increase acetylcholine production and vasodilation; and angiotensin receptor blockers might have anti-amyloidgenic properties (Miners et.al., 2014). Associations of individual drug classes to dementia have been investigated in observational longitudinal studies and clinical trials, which provide the highest quality of evidence for medical decision-making. However, neither source of evidence provides consistent results favoring any one type of anti-hypertensive drug (as
opposed to just BP lowering) as a means to reduce cognitive-related brain disease (Gelber, 2013; Li, 2010; McGuinness, 2009).

Study differences that result in contradictory evidence on lowering blood pressure as a means to reduce cognitive impairment in older persons include: participant age, sample size, choice of outcomes, duration of follow-up, control or stratification for risk moderating exposures, lack of consistency in the drug classes studied, lack of information on important confounders (both current and previous), and the place people are in their trajectories of dementia and changes in systolic and diastolic blood pressure. Further, observational studies based on one cohort may be subject to confounding by indication, which happens when the reason giving (or with-holding) treatment is associated with the outcome. Additionally, such bias could affect comparisons across studies that differ in the prevailing treatment guidelines, and available drug formulary (Klungel, 200; Papanikolaou, 2006; Pencina 2012). The important clinical and public health question of treating elevated BP to reduce the risk of cognitive decline/dementia needs to be addressed with larger samples with a range of health characteristics, who have been followed long term, have detailed measures of brain structure and function, and a standardized approach to analysis.

The analyses for this ancillary study will be based on the Atherosclerosis Risk in Communities (ARIC) Neurocognitive Sub-study (ARIC-NCS), which will be part of a larger meta-analysis of five other population-based cohorts, to investigate the most effective blood pressure treatment to reduce the risk of adverse brain outcomes in older persons.

5. **Main Hypothesis/Study Questions:**

1. Among hypertensive subjects, we hypothesize that lowering hypertension level blood pressure with medications will be associated with less damage to the brain (less atrophy and white matter lesions, fewer infarcts) and lower dementia risk
2. Among normotensive subjects taking medications, no one class of hypertensive medication will be more likely to be associated with damage to the brain or dementia risk
3. Compared to other groups, normotensives who do not take medications have the least cerebral SVD and lowest risk for dementia in late life.

6. **Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).**

Data from the following cohorts will be used: ARIC, AGES-RS, Honolulu Asia Aging Study (HAAS), Framingham Heart Study (FHS), Rotterdam Study, and The Three-City Study.

**Overview**
We used individual participant data from 6 population-based prospective cohort studies, baseline data for which were collected between 1987 and 2006. Except for ARIC, which included ages 45-64 at baseline, each study included more than 500 older adults without dementia at baseline who had blood pressure measurement and information on the use of antihypertensive medication and who had follow-up for at least 5 years. All studies required written informed consent and institutional review board approval.

**Study populations**
All studies recruited community dwelling older people and sought representative samples except for one, which focused on single gender (HAAS). All participating studies worked collaboratively to address issues related to phenotype harmonization, covariate selection and to develop analytic plans for within-study analyses and meta-analysis of results. Briefly, in all...
cohorts, participants were excluded if they lacked information on blood pressure measurements, antihypertensive medication use, had prevalent dementia at baseline, if they were younger than 55 years at baseline or if they had new onset of dementia before the age of 60 years. Individual study goals, recruitment methods, and target populations have been published. Informed consents were obtained from study participants in all studies.

**Definition of antihypertensive drug exposure**

Antihypertensive drugs were grouped by class according to their corresponding Anatomical-Therapeutic-Chemical-Classification system (ATC-code) and included the following: angiotensin-converting enzyme inhibitors (ACEIs), angiotension II receptor antagonist (ARBs), beta blockers, calcium channel blockers (CCBs) (including both long- and short-acting preparations), and diuretics. We considered participants to be included in ACEIs or other 4 core therapeutic drug class as follows: participants were classified as ACEI users if they took ACEI pill in a single or combination preparation, with or without other drug classes. Further participants were classified as pure ACEI users (i.e. on monotherapy with ACEI) if they took ACEI alone.

Drug exposures were assessed by the vials presented at the clinical visit or during the home interview, medication inventory (audit of medical or pharmacy prescription records), or verified self-report. For each analysis, users (or pure users) of a given class were treated as the exposed group, non-drug users or users of all other classes among antihypertensive drug users served as the reference group, respectively. Participants who used multiple drug classes contributed to multiple analyses. Relationships of medications to outcomes will be examined stratified by normal/high blood pressure (>140/90) relative to no medications and for class effect (comparing one class to any other class among those taking antihypertensive medications).

**Diagnosis of incident dementia**

In identifying incident dementia cases, all contributing studies conducted a multi-step procedure. Participants were first screened for possible cognitive impairment using the Mini-Mental State Examination (MMSE) (AGES, FHS, RS, 3C), the 100-point Cognitive Abilities Screening Instrument (CASI) (HAAS), the Digit Symbol Substitution Test (DSSST) (AGES), the Geriatric Mental State schedule (GMS) (RS) or the Isaacs Set Test (IST) (3C). Screen positives based on one or a combination of these tests underwent further diagnostic evaluation. This included more detailed neuropsychological testing (AGES, RS, 3C) and an informant interview about changes in medical history, cognitive function and behavior (AGES, FHS, RS, HAAS, ), as well as a neurological examination (AGES, FHS, RS, 3C, HAAS). Three studies continually monitored participants throughout the study by reviewing medical and mortality records to obtain information on newly diagnosed dementia (AGES, FHS, RS).

A clinical diagnosis of incident dementia was made across studies in accordance to the criteria given in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (ARIC, also for MCI, see below for ARIC details), 4th Edition (DSM-IV) (AGES, FHS, 3C), or DSM-III-R criteria (HAAS, RS). A sub-diagnosis of Alzheimer’s disease was made according to the criteria of the National Institute of Neurological and Communicative Diseases and Stroke Alzheimer's Disease and Related Disorders (NINDS-ADRDA) (AGES, FHS, RS, 3C, HAAS). A sub-diagnosis of vascular dementia was made based on the criteria from the State of California AD Diagnostic and Treatment Centers (AGES, HAAS) or the National Institute of Neurological
Disorders and Stroke and the Association Internationale pour la Recherche et l’Enseignement en Neurosciences (MINDS-AIREN)( FHS, RS, 3C). Participants were allowed to have more than one subtype of dementia given the diagnostic algorithm.

In ARIC, surviving participants at visit 5 (2011-2013) underwent a sequential evaluation; methods have been previously described.[1] The following were administered to all (n=6,471): CES-D, Delayed Word Recall test (DWRT), Digit Symbol Substitution test (DSST), letter fluency test using 3 letters (FAS), which had been administered at previous visits to all (visit 2, visit 4) or a subset (visit 3). In addition, a full neuropsychological battery was administered assessing memory, language, psychomotor speed/executive function, and visuospatial: logical memory immediate and delayed recall, and incidental learning from the Wechsler Memory Scale- III, trail making test parts A and B, WAIS-R digits span backward, Boston naming test, and animal naming. The MMSE was also included. A subset underwent additional testing if any of the following applied: (1) all participants who had undergone an MRI in 2004–2006 as part of the ARIC-MRI study; (2) all participants who had either (a) a low score on MMSE (<21 for whites and <19 for blacks) or (b) who scored <-1.5 Z in any of five cognitive domains and showed definite cognitive decline based on prior delayed word recall task, digit symbol substitution from the WAIS-R, and a letter fluency task scores administered at prior ARIC visits (i.e., lowest 10 percentile on any test or lowest 20th percentile on at least 2 tests); and (3) a random 10% sample of those who did not meet these criteria (i.e., those who were presumed cognitively normal). This subset underwent a neurological exam and structured history, NIH stroke scale, a Hachinski Ischemic scale, a modified uniform Parkinson’s disease rating scale (UPDRS), a clinical dementia rating (CDR) scale by participant and an informant, an informant-provided functional activities questionnaire (FAQ), and Neuropsychiatric Inventory (NPI) and brain MRI. Participants who could attend the in-person exam were offered a telephonic instrument of cognitive status-modified (TICS-m) and if unable to complete the TICS-m, an informant interview. The informant interview was completed primarily where there was suspicion of cognitive impairment or inadequate data to rule it out, more specifically if any of the following was present: (1) follow-up interviewer suspected cognitive impairment, (2) follow-up interviewer reported hearing loss, (3) International Classification of Diseases, Ninth Revision dementia discharge code at any point since the start of cohort surveillance, (4) self-report of dementia diagnosis on the follow-up interview (starting January 1, 2012), (5) proxy contacted for most recent follow-up interview, or if the participant was part of (6) an age comparable random sample of 100 participants not otherwise meeting the mentioned criteria.

Algorithms were developed that defined MCI and dementia according to the National Institute on Aging–Alzheimer’s Association (NIA-AA) workgroups and Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). The algorithm used the following scores: MMSE, the sum of the six individual domain ratings in the CDR (“CDR sum of boxes”), z-scores from the current neuropsychological test battery, and change scores from the serial 3-test ARIC cognitive assessments and the FAQ. Dementia was defined by the following criteria: >1 cognitive domain worse than -1.5 Z-score, a CDR sum of boxes >3 and FAQ >5, and decline below the 10 percentile on one test or below the 20th percentile on two tests in the serial ARIC cognitive battery. In addition, a low MMSE score (<21 for whites or <19 for African-Americans), even in the absence of more complete cognitive testing, was regarded as diagnostic of dementia. MCI diagnosis required at least one domain score worse than 21.5 Z, a CDR sum of
boxes >0.5 and ≤3, an FAQ ≤5, and decline below the 10 percentile on one test or below the 20th percentile on two tests in the serial ARIC cognitive battery. One physician (neurologist or geriatrician) and one neuropsychologist reviewed each case independently and assigned a diagnosis; disagreements were resolved by a third adjudicator. All algorithmic-based diagnosis of “normal or suspected normal cognition” were found to be classified by the clinician reviewer panel as normal; these cases were subsequently only assigned to one reviewer. Etiological diagnoses were also assigned (Alzheimer Disease, Vascular, Lewy-Body disease-related, other) as a primary and if applicable, a secondary etiology, e.g. Alzheimer + vascular.

**Time to event**
Censoring events included diagnosis of dementia, death if it occurred prior to a dementia diagnosis, or no dementia or death by the last follow-up date available. 1. Among participants with incident dementia, time to event was calculated in years from the baseline examination to the diagnosis of dementia; 2. for participants who died, the censor date was the date of death; 3. for participants in whom dementia did not develop, the censor date was the last date on which they were known not to have dementia or the end of follow-up date; 4. for participants with missing or unknown dementia status after baseline examination, time to event was set as 0.

**Statistical analysis**
The analysis will be standardized and run in individual participant data in all contributing studies before pooling across studies by random-effects meta-analysis. The statistical analysis within each study proceeded in 3 steps.

*Step 1: imputation.* To account for missing covariate values across studies, missing values for covariates were imputed using the fully conditional specification method and a total of 5 datasets will be created within each study. As a semi-parametric and flexible approach to missing data, this fully conditional specification method uses a number of chain equations to impute data on a variable-by-variable basis. The imputation model includes all the variables in the subsequent analysis model: age, sex, education level (< high school [0-11 years], high school/GED degree[12 years], some college [≥12 years] and no college degree, college degree and above), any antihypertensive medication use (yes, no), depressive symptomology (GDS-15≥6 vs. <6 or CES-D≥16 vs. <16), eGFR, smoking status (current, former, never), BMI, SBP, DBP, Type 2 diabetes (yes,no), prevalent cardiovascular disease (yes, no), prevalent stroke (no TIA) (yes, no), prevalent atrial fibrillation (yes, no), number of any individual drugs other than antihypertensive medication (0,1,2,3,≥4), incident dementia status (0=censored observation, 1=demented, 2=dead)

*Step 2: analysis.*
*Propensity score model.* To assess the adjusted associations between antihypertensive medication use and risk of incident dementia, a BP-group specific propensity score approach was used to account for confounding by indication. In observational studies, lack of randomization of antihypertensive treatment in dementia outcome research may lead to imbalanced covariates. Consequently, estimation of drug effect can be biased when determinants of antihypertensive treatment are strongly related to adverse outcome of interest. For instance, physicians tend to prescribe more antihypertensives to subjects with greater vascular disease burden or prescribe less antihypertensives to subjects with pre-clinical symptoms of dementia because of fear of diminishing brain perfusion. Thus, it is likely that the beneficial effects of antihypertensives
may be obscured or even appear to be detrimental as a result of channeling of antihypertensives to subjects with the worst diagnosis in the former case, whereas the beneficial effects of antihypertensives could be exaggerated to some extent in the latter case.

On each of these 5 datasets generated in step 1 (imputation), the propensity score was calculated separately for normal (SBP<140 mmHg & DBP<90 mmHg) and high BP (SBP≥140 mmHg or DBP≥90 mmHg) groups, using a logistic regression model with the dependent variable being use of any antihypertensive treatment (yes,no). Independent variables included age, sex, education level, depressive symptomology, eGFR, smoking status, BMI, SBP, DBP, Type 2 diabetes, prevalent cardiovascular disease, prevalent stroke (no TIA), prevalent atrial fibrillation, and number of any individual drugs other than antihypertensive medication. All variables were chosen a priori based on previous publications that were shown to be associated with both antihypertensive treatment and dementia (i.e. confounders).

Cox Proportional Hazards Model:
Cox proportional hazards models were fitted separately to the normal and high BP groups to obtain estimated hazard ratios (HR) and 95% confidence intervals for the association of antihypertensive drug use with risk of dementia and Alzheimer’s disease on each of the 5 imputed datasets. This approach examines the cause-specific hazard of dementia or Alzheimer’s disease and treats the competing event of death as a censoring event. We used age at onset of dementia, death or censoring at the time of the last follow-up as the timescale. A series of models were constructed. Model 1 is adjusted for BP-group specific PS deciles. Model 2 is further adjusted for APOE ε4 carriership (at least one ε4 vs. no ε4 alleles).

Step 3: combining.
We first combined analysis results from the 5 imputed datasets, which were obtained from Cox models in step 2, into one overall result (i.e. pooled HR and 95%CI), separately for normal and high BP-group within each study.

BP-group specific adjusted HRs (models 1-3) were then pooled from all studies using standard random effects meta-analysis. Association tests were performed using the Wald χ² statistic. Heterogeneity across studies was assessed using I² statistic, which measures consistency across studies with the percentage of variance in estimated HRs on the log scale that is attributable to between study variation as opposed to sampling variation. Difference at the study level by design or methods will be investigated by grouping studies by recorded characteristics and by meta-regression.

Sensitivity analysis
1. Subgroup analyses are repeated in strata by age (55-64, 65-74, 75-84, or ≥85 years), by sex and by APOE ε4 carriership (at least one ε4 vs. no ε4 alleles).
2. In order to construct participant groups who had “similar likelihood” of receiving treatment, we first remove those with non-overlapping propensity scores (PS) based on the top (1st) and bottom (99th) percentiles of PS distributions among those being treated and those not being treated, which results in less than 9% study participants across studies being excluded from the following analysis. Second, to access the performance of the PS overlapping and identify potentially non-balanced characteristics, baseline
variables are compared between the treated and non-treated groups after adjusting for overlapping BP-group specific PS deciles. Finally, we repeat Cox proportional hazards analyses using the non-overlapping cohort in normal and high BP groups, respectively. Model 1 is adjusted for BP-group specific PS deciles. Model 2 is further APOE ε4 carriership (at least one ε4 vs. no ε4 alleles). Model 3 adds adjustment for non-balanced baseline covariates between the treated and non-treated groups to model 2, if any is identified within each study.

3. To reduce the possibility of differential antihypertensive prescription or drug intake due to preclinical dementia (which may lead to prodromal changes in BP levels), we rerun analysis after excluding participants who were diagnosed with dementia within 2 years after baseline examination when antihypertensive treatment information was collected.

4. An additional analysis is carried out in a subset of studies treating antihypertensive drug use as a time-dependent variable taking into account the changes in prescription guidelines and availability of antihypertensive drugs over time (3C, RS, etc.?).

5. We additionally evaluate the association of antihypertensive drug use with incident dementia using illness-death models for interval censored data, which accounts for death as a competing risk while dementia is non-terminal (i.e. semi-competing risk regression) as well as the probability of developing dementia between visit and death.

We will use STATA SE 12 (StataCorp, College Station, Texas) for all meta-analytic methods, SAS 9.3/9.4 for 3-step analysis within each study and R package (SmoothHazard) for the estimation of the illness-death model for interval-censored data.

Model 3 adds adjustment for non-balanced baseline covariates between the treated and non-treated groups to model 2, if identified within each study.

7.a. Will the data be used for non-CVD analysis in this manuscript? ___ Yes  x_ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? ___ Yes  ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? _x__ Yes  ____ No APOE E genotype

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”? _x__ Yes  ____ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.csc.c.unc.edu/ARIC/search.php

_x__ Yes  _______ No
10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

- 2175 Gottesman et al. Midlife blood pressure and 20-year cognitive change: The ARIC-Neurocognitive Study
- 2660 Hazzouri, Klopman, Mosley et al. Cardiovascular and metabolic risk, Cognition and Dementia in a Lifecourse Pooled Cohort

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _x_ Yes  ____ No

11.b. If yes, is the proposal

_x_ A. primarily the result of an ancillary study (list number* __2008.06, NCS)
___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PubMed Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

13. Per Data Use Agreement Addendum, approved manuscripts using CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript ____ Yes _x_ No.