1.a. **Full Title:** Diurnal Blood Pressure Variation and Brain Structural Abnormalities in Older Adults.

b. **Abbreviated Title (Length 26 characters):** Nocturnal BP & Brain Health

2. **Writing Group:**
   Writing group members: Timothy Hughes (first author), Rebecca Gottesman (Last/Senior Author), Lynne Wagenknecht, Laura H. Coker and other ARIC investigators are invited.

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

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3. **Timeline:**  
May 2015 – P&P committee  
June – complete ABPM monitoring visits and receive neuroimaging data  
July – finalize data analysis  
September – Draft of manuscript to coauthors

4. **Rationale:**  
Hypertension is arguably the most important modifiable risk factor for stroke, cerebrovascular disease and dementia\(^1\). Mounting evidence from epidemiology studies shows that elevated blood pressure (BP) is a risk factor for incident cognitive decline\(^2\) and dementia\(^3\). Elevated BP is associated with dementia-related pathology, including
cerebrovascular disease and β-amyloid (Aβ) deposition in the brain. The overlap of these two forms of brain pathology lowers the pathologic burden at which cognitive symptoms appear.

The potential mechanisms linking BP and Aβ deposition in the brain remain unclear. BP measured in the clinic has several limitations. When measured in the clinic, BP may be biased (e.g. ‘White-Coat Hypertension’) and cannot represent the complexity of diurnal BP variation. Understanding the diurnal variation in BP especially during sleep may provide valuable clues to the relationship between BP and dementia.

Recent animal and human studies suggest that BP variation during sleep may be an important factor regulating the clearance of Aβ from the brain. Murine models demonstrate that Aβ is cleared from the brain via the flow of cerebrospinal fluid (CSF) along the perivascular space surrounding the vessels of the brain. This flow of CSF is thought to be driven by the pulsatile flow of the pulse wave along the vasculature. Sleep appears to increase the efficiency of this clearance of metabolites from the brain by 60%.

During sleep, the BP normally drops 10-20% with wide ranging effects on cerebrovascular function and cerebral blood flow. This drop in BP is called nocturnal ‘dipping’ and can be assessed by ambulatory BP monitoring (ABPM). Hypertension and greater vascular disease are associated with a lack of nocturnal ‘dipping’ and nocturnal increase in BP during sleep. A lack of normal nocturnal dipping pattern is associated with several adverse cardiovascular and brain outcomes including: left ventricular hypertrophy, myocardial infarction, congestive heart failure, microalbuminuria, cerebrovascular disease and vascular dementia. Less is known about the relationship between nocturnal BP patterns and Aβ deposition.

As part of ancillary study #2014.30, we added 24 hour ABPM to the ARIC-PET study at the Forsyth County field site (n=70). These data allow us to examine the relationship between Aβ deposition and the diurnal variations in BP during sleep. A lack of nocturnal dipping may contribute to impaired Aβ clearance from the brain and age-related cognitive declines among hypertensive older adults. Finally, abnormalities in nocturnal BP may help elucidate the mechanisms linking hypertension to Aβ deposition in the brain.

### 5. Main Hypothesis/Study Questions:

<table>
<thead>
<tr>
<th>24 hour blood pressure pattern</th>
<th>Difference between average sleeping and awake BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dippers (normal)</td>
<td>10-20% lower</td>
</tr>
<tr>
<td>Non-dippers</td>
<td>&lt;10% lower</td>
</tr>
<tr>
<td>Nocturnal increase</td>
<td>&gt;0% higher</td>
</tr>
<tr>
<td>Extreme dippers</td>
<td>&gt;20% lower</td>
</tr>
</tbody>
</table>

H1: Participants with ‘non-dipping’ (<10% decline in nocturnal BP) or nocturnal increases in BP will have greater Aβ deposition in the brain, compared to those with normal nocturnal dipping patterns (10 – 20% decline in BP).

H2: Participants with greater 24-hour average systolic BP and pulse pressure will have greater Aβ deposition in the brain independent of clinic based measurements of BP.

H3: Participants with greater 24-hour average systolic BP and pulse pressure will have evidence of cerebrovascular disease and atrophy on MRI (e.g. white matter hyperintensities, any infarcts, lacunar infarcts, microbleeds, total brain and gray matter atrophy).
H4: ‘Non-dipping’ participants will have higher average 24-hour systolic BP and greater arterial stiffness.

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).

This proposed analysis utilizes cross-sectional data obtained by the ARIC PET study and the ARIC PET ABPM ancillary study among the 70 participants at the Forsyth Co. field center. The two factors for the inclusion criteria of this paper are participation in the (1) florbetapir Aβ-PET imaging and (2) participation in the ABPM substudy. The ABPM study was offered to all ARIC PET at the Forsyth Co. field center. There are no additional exclusion criteria. According to recent population based studies in this age range, we expect that approximately half of the older adults in the ARIC ABPM are ‘non-dippers’ (nocturnal SBP drop <10%) and approximately 30% of ARIC ABPM participants be Aβ-positive for Alzheimer’s disease-like Aβ deposition.

Main Predictor Data
Raw data from the ABPM instruments are processed with propriety software to yield several measures used in the proposed analysis, including individual: mean 24 hr systolic, diastolic and pulse pressure; nocturnal change in BP (% difference from average day BP); and measures of BP variability. Given the small sample size of ~70 ARIC participants, we expect small number of ‘extreme dippers’ and individuals with nocturnal increase in BP. We plan to combine these groups into ‘dippers’ and ‘non-dippers’, respectively for the main analyses.

Main Outcomes
Aβ deposition: (1) Aβ-positivity for Alzheimer’s disease-like Aβ deposition, based on cutpoints for standardized uptake volume ratios (SUVR). A global cortical mean SUVR will be calculated using a weighted average of 9 regions of interest and will be used as the primary outcome. The first part of the analysis will use SUVR as a continuous variable using general linear models and then we will use logistic regression with a cutpoint of SUVR>1.1 to determine Aβ positivity. We will make efforts to keep these analyses consistent with main ARIC-PET analyses. (2) The extent of Aβ deposition using continuous SUVR.
Cerebrovascular disease: (1) white matter hyperintensity volume obtained from ARIC visit 5 MRIs normalized to total intracranial volume; (2) the presence and number of infarcts (e.g. any (y/n) and lacunar (y/n)); (3) the presence and number of cerebral microbleeds, including the presence and number of deep microbleeds; and (4) brain atrophy as estimated from the volume of gray matter relative to the total intracranial volume.

Potential Covariates
Age, gender, cognitive status (adjudicated from ARIC PET and ARIC NCS), diagnosis of hypertension, antihypertensive medications, pulse wave velocity (all from visit 5 or ARIC-PET) and APOE-4 carrier status (if available)

Pulse wave velocity was assessed in the entire cohort at visit 5.

Data Analyses
Unadjusted correlations between ABPM measures and previously obtained measures of Aβ deposition and pulse wave velocity will be assessed with Pearson or Spearman correlation coefficients, where appropriate. We will use ordinary least squares regression to construct multivariable models for the continuous outcomes (e.g. Aβ deposition using SUVR, log transformed white matter hyperintensity volume) and ABPM data as the predictor, adjusted for covariates. Multivariable models will be constructed using logistic regression and the covariates for the following outcomes Aβ positivity (SUVR>1.1), presence of microbleeds and infarcts.

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 (only APOE-4 genotyping)

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.cscce.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)?
There are currently two manuscript proposals with amyloid imaging (Dr. Gottesman’s #2466, #2511). One of these uses the entire ARIC PET cohort to determine the relationships between brain Aβ deposition, midlife hypertension and subclinical vascular risk factors. There are several papers proposals that examine the relationship between blood pressure and brain structure in ARIC (e.g. MS#2351 and MS#1378); however, these ABPM data are unique to my ancillary study proposal. This paper will serve to address the primary aim of this proposal.

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
   ___ A. primarily the result of an ancillary study (list number* 2009.29)
   __ 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.cscce.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.cscce.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.
References