ARIC Manuscript Proposal # 1387

PC Reviewed: 07/08/08	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title:
Temporal changes in blood pressure and cerebral white matter lesions in a biethnic sample: The ARIC MRI study

b. Abbreviated Title (Length 26 characters):
Blood pressure and white matter

2. Writing Group:
Writing group members:
A. Richey Sharrett, Thomas Mosley, Josef Coresh, Kathryn Rose, Diane Catellier, Clifford Jack, Laura Coker, Others welcome

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

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3. Timeline: Analyses to begin as soon as manuscript proposal is approved.
Goal for abstract submission for International Stroke Conference August 11, 2008
Goal is to provide preliminary data for ARIC- NCS submission (October, 2008)

4. Rationale:
Although most emphasis on the relationship between blood pressure and cerebrovascular disease has focused on the increased risk associated with chronic hypertension, there is some evidence that some of this white matter disease may actually be due to hypoperfusion to the

brain. In this way, individuals who are exposed to relative hypotension, over time, compared to their baseline, may be at risk for hypoperfusion to the watershed territories of the brain. Ischemia resulting from this hypoperfusion may lead to infarcts in these watershed territories, contributing to leukoaraiosis, or periventricular white matter disease.

Hypertension, particularly in midlife, is a predictor of later life cerebrovascular disease. An association with white matter disease, which is felt to be at least partially due to small vessel ischemia, has been described in relatively homogeneous populations as part of the Honolulu-Asia Aging Study[1] and the Framingham study.[2] In addition to this positive association, however, there may be an association with lower blood pressures and white matter burden.

Support for the concept that white matter disease may be due to hypoperfusion comes in the form of epidemiologic data as well as histopathologic data. In a pooled set of European cohorts, among 1805 individuals 65 to 75 years of age, both increase in diastolic blood pressure (DBP) and *decrease* in diastolic blood pressure led to an increase in severity of periventricular white matter disease; individuals with a decrease in DBP of at least 2.5 mm Hg per year had an OR of 2.2 (or 4.1, for a more fully adjusted model) for severe periventricular white matter lesions.[3] A similar but nonsignificant relationship was found for a decrease in systolic blood pressure (for every decrease in SBP by 2.5 mm Hg or more per year, the OR's for severe periventricular white matter lesions were 1.2 and 1.9, respectively, in two adjusted models, ns). This J-shaped relationship has also been reported in the Rotterdam study. In that study, individuals with a drop of diastolic blood pressure of at least 10 mm Hg over 20 years had a relative risk of 2.2 (95% CI 1.0, 5.2) for the presence of subcortical white matter lesions.[4] A major limitation of these existing studies is the relative homogeneity of the patient populations in both of these publications. It is not clear if white and black Americans have similar associations with a decrease in blood pressure, from mid-life to later-life, and white matter disease.

Animal models have supported the concept of white matter lesions as due to hypoperfusion.[5] In human autopsy series of subjects with Alzheimer's disease (AD), in determining the contribution of vascular disease to the pathogenesis of AD, many authors have described the presence of watershed microinfarcts. This ischemia in cortical border zones suggests that chronic hypoperfusion contributes to AD,[6, 7] which may be a mechanism for the vascular contribution to this degenerative process.

The mechanism for this potential association between decrease in blood pressure and white matter lesions or cerebral hypoperfusion may be a shift in cerebral autoregulation in individuals with chronic hypertension.[8] The threshold at which cerebral perfusion pressure is compromised varies; the typical cerebral autoregulatory curve is shown in the Figure.

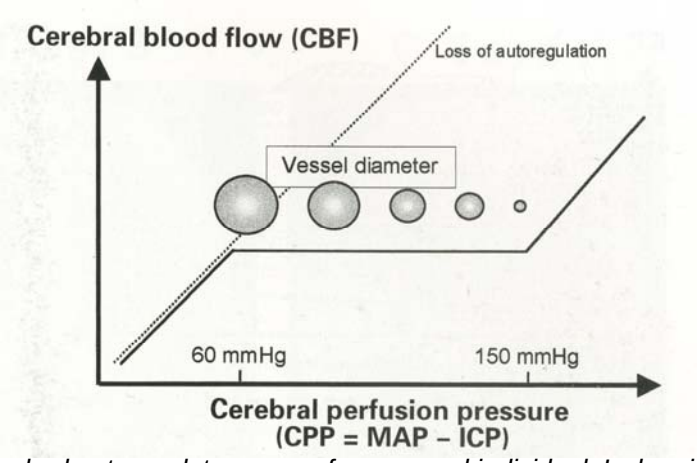

***Figure**. Cerebral autoregulatory curve for a normal individual. Ischemia typically occurs below a cerebral perfusion pressure of 60 mm Hg. Adapted from Bogousslavsky & Caplan, eds., Stroke Syndromes, 2001.*[9]

For an individual without chronic hypertension, ischemia may occur if the cerebral perfusion pressure (CPP) drops below 60 mm Hg. This curve shifts, however, if the individual has hypertension at baseline, leading to a more easily reached threshold below which ischemia occurs. For example, in a chronically hypertensive patient, ischemia may occur at a CPP below 90 mm Hg. The periventricular regions may be most vulnerable, leading to this pattern of leukoaraiosis, because of particularly impaired cerebral blood autoregulation.[10] These regions have been shown, using perfusion MRI, to have decreased cerebral blood flow, compared to other cerebral regions,[11] most likely due to their location in the border zones between major vascular territories of the brain. Other vulnerable regions include the basal ganglia and the hippocampus, which may explain some of the potential role of hypoperfusion in the development and progression of dementia.[12]

An alternative hypothesis to the idea that decrease in blood pressure may lead to ischemia is that chronic hypertension and other atherosclerotic processes leads to increased vessel stiffness, leading to a drop in blood pressure; this has been proposed in studies of the J-shaped relationship between diastolic blood pressure and aortic atherosclerosis.[13]

The public health concern regarding this possible role of hypoperfusion to the brain in individuals exposed to relative hypotension is that some patients, with chronic hypertension, may be treated too aggressively for their hypertension and this may contribute to chronic white matter ischemia and eventually cognitive problems. Results from clinical trials on antihypertensives which have followed cognition have showed heterogeneous results in those with moderate reduction in blood pressure,[14] perhaps due to some individuals actually worsening with aggressive reductions. It is probably important to distinguish between a natural decrease in blood pressure, such as may be due to changes in vascular stiffness, or an iatrogenic decrease due to antihypertensive treatment.This may be an even greater concern in individuals with pre-existing cerebrovascular disease, as they may be particularly vulnerable to further hypoperfusion.[15] In a small series of individuals undergoing coronary artery bypass graft (CABG) surgery, who had other vascular risk factors, decrease in blood pressure from before to after surgery was associated with a decrease in cognitive test performance.[16]

In addition to hypoperfusion due to temporal decreases in blood pressure, an additional role may be played by recurrent hypoperfusion due to orthostatic hypotension. Orthostatic hypotension has been previously associated with incident ischemic stroke[17] in the ARIC study and may predict white matter burden.[18]

The role of a drop in blood pressure on white matter lesion progression may differ based on race. It has been reported that blacks of African descent (in the United Kingdom), with comparable blood pressures to whites through ambulatory monitoring, had greater amounts of parieto-occipital white matter lesions, even after adjustment for other vascular risk factors. This may be because of more chronic hypertension at times before the monitoring, which could cause white matter lesions through ischemia itself, or could lead to ultimate hypoperfusion when blood pressure is lowered to an appropriate clinical range.[19] In addition, there tends to be more intracranial atherosclerosis in blacks, compared to whites, which could make the brain even more susceptible to relative hypotension. The ARIC population, which is virtually 50% black and 50% white, is well suited to pursue questions on the importance of fluctuations in blood pressure from baseline in both black and white individuals.

5. Main Hypothesis/Study Questions:

1. Blood pressure will be associated with white matter lesion volume. This association will be explored for blood pressures from: visit 1, visit 2, visit 3, visit 4, average of these 4, ARIC Brain MRI visit, and (ARIC Brain MRI minus the average). The strongest association will be with blood pressure in visit 1, with weakest associations with the concurrent BP.

2. Presence of orthostatic hypotension at visit 1 (defined previously in ARIC studies as a decrease in SBP>=20 mm Hg and/or a decrease in DBP>=10 mm Hg, associated with changing from the supine to the standing position) will be associated with white matter lesion volume.
3. A change from normotensive (at visit 1) to hypotensive-range blood pressures at the Brain MRI visit (over 15-18 years) will be associated with higher white matter volume.

a. When stratified by use of blood pressure treatment, both those with and without treatment who experience this change from normotension to hypotension will have higher white matter volumes.

b. When stratified and adjusted for comorbidity such as malignancy and history of MI, the association between change to hypotension and white matter volume will persist only among those individuals on blood pressure medications.

c. The association will be strongest for individuals who have a shift in their *diastolic* blood pressure from a normotensive to hypotensive range, based on previous studies.

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).

Study Design: prospective data collection on risk factors with cross-sectional definition of the outcome based on the ARIC Brain MRI in 2004-2006.
Inclusion: All individuals in the ARIC Brain MRI cohort.
Exclusion: Missing Brain MRI data; Missing Brain MRI Blood pressure data (for the hypotheses involving Brain MRI BP data)
Data Analysis:
Hypothesis 1: Linear regression with blood pressures at visit 1,2,3,4,brain MRI, average, current minus average each in separate models (independent variables), predicting white matter volume (dependent variable). Adjusting for age, diabetes, hyperlipidemia.
Hypothesis 2: Linear regression; OH presence/ absence (independent variable), WM volume (dependent variable).
Hypothesis 3: Linear regression: Change from normotensive to hypotensive: both as categorical variable (y/n) and continuous (amount of change in BP) (independent variable), WM volume (dependent variable). Adjust for average BP over ARIC visits 1-4, other confounders including weight loss, new use of hemodialysis, history of CABG surgery. I will stratify the analysis for those on BP treatment vs those without BP treatment.
I will also consider a linear spline model with 1-2 knots representing changes in the relationship between decrease in blood pressure and white matter lesion volume to explore potential points at which association changes.

Outcome: White matter lesions: Volume (measured volumetrically) and white matter grade.
Variables of interest: Blood pressure: visits 1, 2, 3, 4, Brain MRI visit
White matter: Brain MRI visit #2 (2004-2006)
Other potential confounders: Weight loss (from visit 1 to ARIC Brain MRI visit), history of CABG surgery, new use of hemodialysis.

Limitations: It may be that this concern about a shift from normotension to hypotension only applies to a subset of individuals, e.g. those with white matter disease before exposed to a drop in blood pressure. Because we don't have a brain MRI from the first blood pressure point (visit 1), it may be difficult to identify this subset. In addition, looking at discrete blood pressure points over time (visit 1, brain MRI visit) may not capture fluctuations in blood pressure over this time that could lead to cerebral hypoperfusion.

There are numerous potential confounders that may cause someone to become hypotensive; I will attempt to adjust for these (such as history of MI, malignancy, etc.).

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 ICTDER03 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? ____ Yes _X_ No

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"?
____ Yes ____ No

8.c. If yes, is the author aware that the participants with RES_DNA = 'not for profit' restriction must be excluded if the data are used by a for profit group?
____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.cscc.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)? MP 314 "Cerebral abnormalities identified on magnetic resonance imaging and cognitive functioning: The ARIC Study", 1104: "Orthostatic

hypotension and cognitive function: the ARIC study", 270A: "Postural change and blood pressure, variation due to gender and race", 734: "Blood pressure over time and changes in cognitive function", 336: "Association of cerebral white matter lesions to hypertension, its treatment and control- the ARIC study"

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* ARIC Brain MRI:__1999.01_____)

___ 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/

12. 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.

References

1. Havlik RJ, Foley DJ, Sayer B, Masaki K, White L, Launer LJ. Variability in midlife systolic blood pressure is related to late-life brain white matter lesions. *Stroke*. 2002;33:26-30
2. Jeerakathil T, Wolf PA, Beiser A, Massaro J, Seshadri S, D'Agostino RB, DeCarli C. Stroke risk profile predicts white matter hyperintensity volume. The framingham study. *Stroke*. 2004;35:1857-1861
3. van Dijk EJ, Breteler MM, Schmidt R, Berger K, Nilsson L-G, Oudkerk M, Pajak A, Sans S, de Ridder M, Dufouil C, Fuhrer R, Giampaoli S, Launer LJ, Hofman A. The association between blood pressure, hypertension, and cerebral white matter lesions. *Hypertension*. 2004;44:625-630
4. de Leeuw FE, de Groot JC, Oudkerk M, Witteman JC, Hofman A, van Gijn J, Breteler MM. A follow-up study of blood pressure and cerebral white matter lesions. *Ann Neurol*. 1999;46:827-833
5. Kurumatani T, Kudo T, Ikura Y, Takeda M. White matter changes in the gerbil brain under chronic cerebral hypoperfusion. *Stroke*. 1998;29:1058-1062
6. Suter O-C, Sunthorn T, Kraftsik R, Straubel J, Darekar P, Khalili K, Miklossy J. Cerebral hypoperfusion generates cortical watershed microinfarcts in alzheimer disease. *Stroke*. 2002;33:1986-1992
7. Miklossy J. Cerebral hypoperfusion induces cortical watershed microinfarcts which may further aggravate cognitive decline in alzheimer's disease. *Neurol Res*. 2003;25:605-610
8. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev*. 1990;2:161-192
9. Schwarz S, Schwab S, Hacke W. Large and panhemispheric infarcts. In: Bogousslavsky J, Caplan LR, eds. *Stroke syndromes*. Cambridge, UK: Cambridge University Press; 2001:490-498.
10. Matsushita K, Kuriyama Y, Nagatsuka K, Nakamura M, Sawada T, Omae T. Periventricular white matter lucency and cerebral blod flow autoregulation in hypertensive patients. *Hypertension*. 1994;23:565-568
11. O'Sullivan M, Lythgoe DJ, Pereira AC, Summers PE, Jarosz JM, Williams SC, Markus HS. Patterns of cerebral blood flow reduction in patients with ischemic leukoaraiosis. *Neurology*. 2002;59:321-326
12. Roman GC. Brain hypoperfusion: A critical factor in vascular dementia. *Neurologic Research*. 2004;26:454-458

13. Witteman JC, Grobbee DE, Valkenburg HA, van Hemert AM, Stijnen T, Burger H, Hofman A. J-shaped relation between change in diastolic blood pressure and progression of aortic atherosclerosis. *Lancet*. 1994;343:504-507
14. Birns J, Morris R, Donaldson N, Kalra L. The effects of blood pressure reduction on cognitive function: A review of effects based on pooled data from clinical trials. *J Hypertens*. 2006;24:1907-1914
15. Birns J, Markus H, Kalra L. Blood pressure reduction for vascular risk: Is there a price to be paid? *Stroke*. 2005;36:1308-1313
16. Gottesman RF, Hillis AE, Grega MA, Borowicz Jr. LM, Selnes OA, Baumgartner WA, McKhann GM. Early postoperative cognitive dysfunction and blood pressure during coronary artery bypass grafting. *Arch Neurol*. 2007;64:epub early online http://archneur.ama-assn.org/cgi/content/short/64.68.noc70028v70021
17. Eigenbrodt ML, Rose KM, Couper DJ, Arnett DK, Smith R, Jones D. Orthostatic hypotension as a risk factor for stroke: The atherosclerosis risk in communities (aric) study. *Stroke*. 2000;31:2307-2313
18. Roman GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. *Lancet Neurol*. 2002;1:426-436
19. Birns J, Morris R, Jarosz J, Markus H, Kalra L. Ethnic differences in the cerebrovascular impact of hypertension. *Cerebrovasc Dis*. 2008;25:408-416