ARIC Manuscript Proposal #2334

PC Reviewed: 3/11/14	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Troponin T and N-terminal pro-B-type Natriuretic Peptide and Cognitive Decline and Dementia in the ARIC study

b. Abbreviated Title (Length 26 characters): **Cardiac Biomarkers & Cognition**

2. Writing Group:
Writing group members:

Yashashwi Pokharel
Melinda Power
Andrea L. C. Schneider
Andrea M. Rawlings
Elizabeth Selvin
Wensheng Sun
Vijay Nambi
Salim Virani
David Knopman
Ron Hoogeveen
Lisa Wruck
Alvaro Alonso
Gerardo Heiss
Rebecca Gottesman
Josef Coresh
Thomas Mosley
Christie Ballantyne

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

First author: Yashashwi Pokharel
Address: Baylor College of Medicine
6565 Fannin Street,
MS A601/ STE B160
Houston, TX 77030
Phone: 713-798-5800
Fax: 713-798-7885
E-mail: yashashwi.pokharel@bcm.edu

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: Christie Ballantyne
Address: Baylor College of Medicine,
6565 Fannin Street,
MS A601/ STE B160
Houston, TX 77030
Phone: 713-798-7545
Fax: 713-798-7885
E-mail: cmb@bcm.edu

3. Timeline: Analysis to start as soon as approval is obtained. Manuscript is to be prepared as soon as analyses are available. The analysis and manuscript preparation will take place within 1 year from approval of the proposal.

4. Rationale:

Dementia affects about 14.7% of people ≥ 70 years of age[1] and is the 6th leading cause of death in the US.[2] In 2010, the total monetary cost of dementia was between $157 and $215 billion.[1] Cardiovascular disease (CVD)[3-12] is associated with dementia and cognitive decline. The association is particularly strong after a clinical stroke[13] or subclinical vascular brain injury.[13-15] Cerebrovascular disease is also associated with pathologically confirmed Alzheimer's disease (AD).[16,17] Cardiac troponin T, as measured by highly sensitive assay (hs-cTnT), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are both associated with incident cardiovascular (CV) disorders,[18-24] including stroke[21,22] and subclinical brain injury.[25,26] hs-cTnT[27] and NT-proBNP[28] are sensitive biomarker of myocardial injury and stretch respectively. Their association with stroke likely reflects coexisting subclinical cardiac end organ damage and shared risk factors resulting in microvascular dysfunction, or yet other unidentified mechanisms. Since increasing levels of both hs-cTnT and NT-proBNP were shown to have significant trend for clinical[21] and subclinical brain injury[26] in the ARIC study, probably reflecting increasing burden of underlying disease and risk factors with higher levels of biomarkers, it is plausible that increasing levels of these biomarkers over time may be associated with enhanced cognitive loss and dementia. A recent analysis from ARIC based study (MS# 2002, currently *in-press* in *European Heart Journal)* showed that increasing hs-cTnT levels at visit 4 were associated with lower cognitive scores at visit 4, and decline in cognitive scores between visits 2 and 4. In addition, higher hs-cTnT levels were also associated with increased risk for dementia hospitalization, including hospitalization for vascular dementia, but not for Alzheimer's dementia. The dementia outcome was based on *ICD-9* diagnosis codes. Dementia leading to hospitalization usually occurs in severe cases, and therefore a significant portion of "milder" dementia cases may have been missed with this approach. Furthermore, using hospitalization diagnostic codes may not be specific to accurately differentiate between vascular dementia and Alzheimer's disease.

Neurocognitive data were collected at visits 4 and 5 by trained examiners following standard protocols. Cognitive decline was assessed using scores on the Delayed Word Recall

Test (DWRT), Digit-Symbol Substitution Test (DSST) and Word Fluency Test (WFT) at ARIC visits 4 and 5, and a global score summarizing performance on these three tests. DWRT, DSST and WFT are tests of recent memory; executive function and processing speed; and of expressive language, respectively.[29] Higher scores reflect better cognitive function. Unmeasured confounders like cultural factors are less likely to influence changes in cognitive scores based on serial cognitive tests.[30] At visit 5, ARIC neurocognitive study (NCS) ascertained and diagnosed MCI, dementia and its subtypes based on a rigorous process including, but not limited to performance on tests of several cognitive domains, with standardization using age, education, and race-based norms, informant interview using the Clinical Dementia Rating Scale, and expert adjudication for the presence of normal cognition, MCI and dementia, as well as subtypes. For those who did not attend visit 5, additional dementia and MCI cases are currently being identified with information obtained by telephone interview, informant interview, hospitalization ICD-9 codes or diagnoses from the Medicare billing claims database. Therefore ARIC visit 5th provides an opportunity to assess a more clear and comprehensive neurocognitive information on the association of cardiac biomarkers with dementia and its sub-types. In addition, we will be able to examine the prospective association of change in cognitive function between visits 4 and 5. Further we did not find any published data on the association of patterns in the long-term changes of cardiac biomarkers with dementia, mild cognitive impairment (MCI) and cognitive decline. Therefore we propose to evaluate the relationship of hs-cTnT and NT-proBNP to cognitive decline, MCI and dementia in about 6,538 ARIC participants in their 7th to 9th decades of life who attended visits 4 and 5**.** We will also test associations of pattern of changes in hs-cTnT with cognitive decline (between visits 4 and 5), and MCI and dementia at visit 5.

5. Main Hypothesis:

a. Higher levels of cardiac biomarkers (hs-cTnT and NT-proBNP) are associated with increased risk of cognitive decline, dementia or MCI, with a stronger association for the vascular component.
b. Individuals who have increasing hs-cTnT from visit 4 to 5 have higher risk of cognitive decline, dementia and MCI than individuals with normal, stable, or decreasing levels from visit 4 to 5, with a stronger association for the vascular component.

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).

Variables:

Information on covariates, including but not limited to demographics, blood lipids, vascular risk factors and other health conditions, socioeconomic indicators, apo-lipoprotein (APO) E genotype status was obtained at visit 4, except for education, which was obtained at visit 1.

Inclusion and exclusion criteria:

All ARIC participants attending both visits 4 and 5 will be included. We will exclude those with missing information on the biomarkers, education, cognitive test, MCI and dementia; prevalent dementia, TIA, stroke and CHD at visit 4; neurological conditions at visits 4 or 5 that may confound incident dementia diagnosis, such as multiple sclerosis, Parkinson's disease, brain tumor, cranial radiation and surgery; individuals with low cognitive scores (lowest 5%) on each test at visit 4 to exclude possible prevalent dementia.[29,31]

Independent variable:

Cardiac biomarkers hs-cTnT and NTpro-BNP at visit 4 and and changes in hs-cTnT levels between visits 4 and 5 (see below in analysis).

Dependent variable:

Changes in test specific (DWRT, DSST and WFT) and global Z-scores at visits V4 and V5; and visit 5 adjudicated diagnoses of dementia or MCI and its subtypes. We will allow for additional dementia cases currently being ascertained using various methods as described above.

Analysis plan:

We will test the association of biomarkers with changes in test specific (DWRT, DSST and WFT) and global Z-scores between visits 4 and 5 using linear regression model. Ordinal logistic regression analysis will be used to compare normal cognition, MCI and dementia. Proportional odds assumption will be verified, and if not satisfied, we will consider using multinomial logistic model. Comparison will be using per standard deviation increase and alternatively using tertile-based analysis of the biomarkers. In a multivariate model, adjustment will be made for age, gender, race/ARIC site, education, occupation, area-level socioeconomic status (SES), diabetes, APOE genotype status, hypertension, total cholesterol/HDL-C, statin use, BMI, a summary of healthy diet, physical activity, health care utilization variables, alcohol use and smoking. Race, gender, time in study and education each will be assessed as effect modifiers, and if significant interaction is present, we will consider a stratified analysis. Furthermore, in sensitivity analysis we will exclude individuals who develop CHD or stroke between visits 4 and 5. We will also consider using changes in raw cognitive test score as our outcome. We will repeat the analysis after excluding those with lowest 5% cognitive scores on each test at visit 4 to assess the effect of removing scores that have restricted ability to show decline. In additional analysis, we will consider analysis by categorizing independent variable (hs-cTnT) based on limit of measurement (hs-cTnT <3 ng/dL). Analysis will be coordinated with the ARIC NCS analysis workgroup.

Visit 4	Visit 5	Change
<5 ng/dL	<5 ng/dL	Normal
	≥5 ng/dL	Increase
≥5	>50%	Increase

ng/dL	>50%	Decrease
	≤50% change	Stable

To test the effect of changes in the hs-cTnT we will categorize hs-cTnT based on limit of detection (<5ng/dL). At visit 4, if the level is not detectable (i.e. <5 ng/dL), possible changes at visit 5 include still not detectable (normal) or ≥5 ng/dL (increase). At visit 4, if the level is ≥5 ng/dL, possible changes at visit 5 are >50% increase (increase), >50% decrease (decrease) or <50% change (stable) (table).[18,32,33] Ordinal logistic regression analysis will be used to compare normal cognition, MCI and dementia. Based on results of analysis for baseline hs-cTnT and cognitive change or dementia if those with detectable hs-cTnT at visit 4 have increased risk for cognitive decline or dementia than those without, for analysis for change in hs-cTnT we will use two distinct analyses based on whether hs-cTnT at visit 4 is detectable or not. (1) For individuals with not detectable levels of hs-cTnT at visit 4, the reference will be the group that still remained not detectable at visit 5 (normal); (2) those with detectable levels at visit 4, the reference will be the group that decreased at visit 5. We will also compare trends across various groups. A multivariate model will be developed similar to above. Race and gender each will be assessed as effect modifiers, and if significant interaction is present, we will consider a stratified analysis. In sensitivity analysis, we will consider analysis by categorizing independent variable based on limit of measurement (<3 ng/dL). We will also consider tertile-based analysis after developing appropriate tertiles of the hs-cTnT changes between visits 4 and 5. This strategy will treat changes in biomarker as a continuous variable and may improve statistical power. In addition, it will incorporate the risk associated with disproportionate increase or decrease in hs-cTnT in the group with already high levels of biomarkers at visit 4, as this particular pattern of change could reflect a different biology than non-disproportionate changes.

We know that changes in NT-proBNP exhibits significant biologic variability, as found both inside (unpublished data) and outside[34,35] ARIC study. Therefore we will perform exploratory analysis of patterns of changes in NT-proBNP with cognitive change and risk of dementia or MCI using similar approach as for changes in hs-cTnT.

Potential problem and alternate strategy: ARIC visit 5 participants could represent a healthier subcohort of the visit 4 cohort, and this can possibly introduce bias. We will compare participants' characteristics from visits 4 and 5. We will also consider inverse probability of attrition weighting, where we will create logistic regression models to predict death and/or drop-out between visits 4 and 5. The predicted probability of attrition is then used to weight up people who make it to visit 5 to account for people who did not.

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? ____ 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

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)?

MS# 2002. Association of High-Sensitivity Cardiac Troponin T (hs-cTnT) with Cognitive Function: the Atherosclerosis Risk in Communities 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

___ A. primarily the result of an ancillary study (list number* _____)

_X_ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* 2014.04)

*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.

1. Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary costs of dementia in the United States. *The New England journal of medicine.* Apr 4 2013;368(14):1326-1334.
2. Thies W, Bleiler L. 2013 Alzheimer's disease facts and figures. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* Mar 2013;9(2):208-245.
3. Douiri A, McKevitt C, Emmett ES, Rudd AG, Wolfe CD. Long-term effects of secondary prevention on cognitive function in stroke patients. *Circulation.* Sep 17 2013;128(12):1341-1348.
4. Douiri A, Rudd AG, Wolfe CD. Prevalence of poststroke cognitive impairment: South London Stroke Register 1995-2010. *Stroke; a journal of cerebral circulation.* Jan 2013;44(1):138-145.
5. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. *Lancet neurology.* Nov 2009;8(11):1006-1018.
6. Sharp SI, Aarsland D, Day S, Sonnesyn H, Ballard C. Hypertension is a potential risk factor for vascular dementia: systematic review. *International journal of geriatric psychiatry.* Jul 2011;26(7):661-669.
7. Toledo JB, Arnold SE, Raible K, et al. Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. *Brain : a journal of neurology.* Sep 2013;136(Pt 9):2697-2706.
8. Reis JP, Launer LJ, Terry JG, et al. Subclinical atherosclerotic calcification and cognitive functioning in middle-aged adults: the CARDIA study. *Atherosclerosis.* Nov 2013;231(1):72-77.
9. Wendell CR, Waldstein SR, Ferrucci L, O'Brien RJ, Strait JB, Zonderman AB. Carotid atherosclerosis and prospective risk of dementia. *Stroke; a journal of cerebral circulation.* Dec 2012;43(12):3319-3324.
10. Arntzen KA, Schirmer H, Johnsen SH, Wilsgaard T, Mathiesen EB. Carotid atherosclerosis predicts lower cognitive test results: a 7-year follow-up study of 4,371 stroke-free subjects - the Tromso study. *Cerebrovascular diseases (Basel, Switzerland).* 2012;33(2):159-165.
11. Yukutake T, Yamada M, Fukutani N, et al. Arterial Stiffness Determined According to the Cardio-Ankle Vascular Index (CAVI) is Associated with Mild Cognitive Decline in Community-Dwelling Elderly Subjects. *Journal of atherosclerosis and thrombosis.* Sep 10 2013.
12. Makin SD, Turpin S, Dennis MS, Wardlaw JM. Cognitive impairment after lacunar stroke: systematic review and meta-analysis of incidence, prevalence and comparison with other stroke subtypes. *Journal of neurology, neurosurgery, and psychiatry.* Aug 2013;84(8):893-900.
13. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the american heart association/american stroke association. *Stroke; a journal of cerebral circulation.* Sep 2011;42(9):2672-2713.
14. Roher AE, Tyas SL, Maarouf CL, et al. Intracranial atherosclerosis as a contributing factor to Alzheimer's disease dementia. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* Jul 2011;7(4):436-444.

15. Yarchoan M, Xie SX, Kling MA, et al. Cerebrovascular atherosclerosis correlates with Alzheimer pathology in neurodegenerative dementias. *Brain : a journal of neurology.* Dec 2012;135(Pt 12):3749-3756.

16. Snowdon DA, Greiner LH, Mortimer JA, Riley KP, Greiner PA, Markesbery WR. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. *JAMA : the journal of the American Medical Association.* Mar 12 1997;277(10):813-817.

17. Bennett DA, Wilson RS, Arvanitakis Z, Boyle PA, de Toledo-Morrell L, Schneider JA. Selected findings from the Religious Orders Study and Rush Memory and Aging Project. *Journal of Alzheimer's disease : JAD.* 2013;33 Suppl 1:S397-403.

18. deFilippi CR, de Lemos JA, Christenson RH, et al. Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults. *JAMA : the journal of the American Medical Association.* Dec 8 2010;304(22):2494-2502.

19. Di Angelantonio E, Chowdhury R, Sarwar N, et al. B-type natriuretic peptides and cardiovascular risk: systematic review and meta-analysis of 40 prospective studies. *Circulation.* Dec 1 2009;120(22):2177-2187.

20. Eggers KM, Al-Shakarchi J, Berglund L, et al. High-sensitive cardiac troponin T and its relations to cardiovascular risk factors, morbidity, and mortality in elderly men. *American heart journal.* Sep 2013;166(3):541-548.

21. Folsom AR, Nambi V, Bell EJ, et al. Troponin T, N-terminal pro-B-type natriuretic peptide, and incidence of stroke: the atherosclerosis risk in communities study. *Stroke; a journal of cerebral circulation.* Apr 2013;44(4):961-967.

22. Oluleye OW, Folsom AR, Nambi V, Lutsey PL, Ballantyne CM. Troponin T, B-type natriuretic peptide, C-reactive protein, and cause-specific mortality. *Annals of epidemiology.* Feb 2013;23(2):66-73.

23. Saunders JT, Nambi V, de Lemos JA, et al. Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study. *Circulation.* Apr 5 2011;123(13):1367-1376.

24. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *The New England journal of medicine.* Feb 12 2004;350(7):655-663.

25. Pikula A, Beiser AS, DeCarli C, et al. Multiple biomarkers and risk of clinical and subclinical vascular brain injury: the Framingham Offspring Study. *Circulation.* May 1 2012;125(17):2100-2107.

26. Dadu RT, Fornage M, Virani SS, et al. Cardiovascular biomarkers and subclinical brain disease in the atherosclerosis risk in communities study. *Stroke; a journal of cerebral circulation.* Jul 2013;44(7):1803-1808.

27. Reichlin T, Hochholzer W, Bassetti S, et al. Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *The New England journal of medicine.* Aug 27 2009;361(9):858-867.

28. Hall C. Essential biochemistry and physiology of (NT-pro)BNP. *European journal of heart failure.* Mar 15 2004;6(3):257-260.

29. Schneider AL, Sharrett AR, Patel MD, et al. Education and cognitive change over 15 years: the atherosclerosis risk in communities study. *Journal of the American Geriatrics Society.* Oct 2012;60(10):1847-1853.

30. Glymour MM, Weuve J, Berkman LF, Kawachi I, Robins JM. When is baseline adjustment useful in analyses of change? An example with education and cognitive change. *American journal of epidemiology.* Aug 1 2005;162(3):267-278.

31. Alonso A, Mosley TH, Jr., Gottesman RF, Catellier D, Sharrett AR, Coresh J. Risk of dementia hospitalisation associated with cardiovascular risk factors in midlife and older age: the Atherosclerosis Risk in Communities (ARIC) study. *Journal of neurology, neurosurgery, and psychiatry.* Nov 2009;80(11):1194-1201.

32. White HD, Tonkin A, Simes J, et al. Association of contemporary sensitive troponin I levels at baseline and change at 1 year with long-term coronary events following myocardial infarction or unstable angina: Results from the LIPID study. *Journal of the American College of Cardiology.* Oct 17 2013.

33. Wu AH, Lu QA, Todd J, Moecks J, Wians F. Short- and long-term biological variation in cardiac troponin I measured with a high-sensitivity assay: implications for clinical practice. *Clinical chemistry.* Jan 2009;55(1):52-58.

34. Fradley MG, Larson MG, Cheng S, et al. Reference limits for N-terminal-pro-B-type natriuretic peptide in healthy individuals (from the Framingham Heart Study). *The American journal of cardiology.* Nov 1 2011;108(9):1341-1345.

35. Melzi d'Eril G, Tagnochetti T, Nauti A, et al. Biological variation of N-terminal pro-brain natriuretic peptide in healthy individuals. *Clinical chemistry.* Sep 2003;49(9):1554-1555.