ARIC Manuscript Proposal #1564

PC Reviewed: 10/13/09	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Correlation of High Sensitivity Troponin-T (hs-cTnT) and Amino Terminal pro-Brain Natriuretic Peptide (NT-proBNP) with Renal Function Parameters; and Association with Mortality and Adverse Cardiovascular Events

b. Abbreviated Title (Length 26 characters): hs-cTnT, NT-proBNP and Renal Function

2. Writing Group:

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

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3. **Timeline**: Analysis is to start as soon as approval is obtained. Manuscript is to be prepared as soon as analysis is available. We anticipate that the manuscript will be prepared within one year from approval of the analysis.

4. **Rationale**:

Renal dysfunction is an independent predictor of mortality in patients with ACS (Al Suwaidi et al. 2002, Aviles et al. 2002), and can cause of elevated serum NT-proBNP and cTn levels without overt congestive heart failure (CHF) or acute coronary syndrome (ACS) (Wu et al. 2007). In asymptomatic patients with advanced renal failure, elevated cTn and NT-proBNP predict mortality, but the significance of these elevations in mild or moderate renal dysfunction is not known (Apple et al. 2002, Apple et al. 2004). While elevated levels of cTnT and NT-proBNP identify patients with known cardiovascular disease who are high risk of adverse outcomes (de Lemos et al. 2001, Omland et al. 2002, Peacock et al. 2008), it is not known if there should be different threshold cutoffs for patients with abnormal renal function.

In addition to creatinine, several other markers of renal function have prognostic significance. Cystatin C has a linear association with cardiovascular risk, compared to creatinine, which exhibits a threshold effect below an estimated creatinine clearance of 60mL/min/1.73m^2 (Shlipak et al. 2005, Shlipak et al. 2006). Cystatin C depends on GFR, but is less dependant on age, race, and gender than creatinine (Stevens et al. 2009), and correlates better experimentally with GFR than does creatinine (Fliser and Ritz 2001). Urinary albumin excretion also predicts cardiovascular outcomes in patients with mild-moderate impairment of creatinine clearance (Brantsma et al. 2008, Kistorp et al. 2005). In addition to cystatin C and urinary albumin excretion, β_2- microglobulin predicts early onset atherosclerosis and mortality in hemodialysis patients (Zumrutdal et al. 2005, Okuno et al. 2009). B-trace protein is another novel renal analyte that has been correlated with GFR (Priem et al. 1999), and has been shown to be predictive of the extent of coronary atherosclerosis by angiogram in patients undergoing elective cardiac catheterization (Inoue et al. 2008). Despite the association between these markers of renal function and adverse cardiovascular outcome, the correlation between troponin, NT-proBNP and these various markers of renal function is not clear. In a recent study using multiple biomarkers, the combination of cardiac troponin, NT-proBNP, and cystatin C identified high risk patients, but the correlation between these markers was not assessed (Keller et al. 2009, Zethelius et al. 2008).

A novel high sensitivity cardiac troponin-T assay, which can detect circulating levels of troponin-T at 10 fold lower concentrations than 4th generation assays, is being measured from stored plasma samples from the ARIC study visit 4 along with NT-proBNP, cystatin C, and other markers of renal function. The recent study by Reichlin et al. highlighted the improved performance of this hs-cTnT assay in diagnosis of an MI, and that this accuracy persisted in patients with a moderate degree of renal insufficiency (Reichlin et al. 2009). We propose analysis of the correlation between hs-cTnT and NT-proBNP with various measures of renal function, and also examination of the effect of various markers of renal dysfunction on the ability of hs-cTnT and NT-pro BNP to predict cardviovascular outcomes.

5. Main Hypothesis/Study Aims:

a. We aim to quantify the correlation between hs-cTnT and NT-proBNP with various markers of renal function (creatinine, cystatin C, urinary microalbuminuria)
b. The addition of measurements of renal function will attenuate the predictive value of hs-cTnT
c. The optimal threshold levels of hs-cTnT and NT-proBNP to predict mortality and cardiovascular outcomes will be higher in individuals with renal dysfunction than those with normal renal function

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).

1. After standard ARIC exclusions, subjects from ARIC visit 4 will be eligible. We will exclude those individuals without measures of serum creatinine, or without measures of urinary albumin and urinary creatinine.
    a. We will examine individuals with and without prevalent CVD separately
2. We will first examine the correlation between variables using Spearman Rank Correlation for the following combinations
    a. hs-cTnT with cystatin C, creatinine, urinary microalbumin
    b. NT-proBNP with cystatin C, creatinine, urinary microalbumin
3. We will then assess the effect modification of varying levels of renal function on the predictive power of hs-cTnT and NT-proBNP
    a. We will perform separate analysis for individuals with and without prevalent CVD, and stratify individuals on the basis of renal function parameters as follows:

b. Highly sensitive cardiac Troponin-T will be modeled as both a continuous variable and as a categorical variable reported as quartiles in the detectable range (≥ 3pg/mL to ≤10,000 pg/mL)

c. NT-proBNP levels will be modeled as both continuous variable and categorical variable (by quartiles)

   i. We will assess the effect of varying levels of renal function on the association between hs-cTnT and NT-proBNP and cardiovascular events (both as individual and composite measures).

      1. CV death, Hospitalization for CHF, Hospitalized MI or fatal CHD or coronary revascularization procedure, Hospitalized CVA or fatal stroke, Hospitalized unstable angina (ICD-9 411.1)

d. Renal function parameters will be modeled both continuously and categorically

   i. Creatinine Clearance by MDRD Study equation, and CKD-Epi equation - separated into CKD stages I-V by eGFR according to K/DOQI guidelines

   ii. Cystatin C levels and eGFR by cystatin also separated into CKD stages I-V

   iii. Urinary Albumin/Creatinine ratio (above or below 30 mg/ 24 hours)

   iv. The effect of renal function on the association between hs-cTnT and NT-proBNP will be tested using interaction terms in Cox-proportional hazards models adjusted for: Age, gender, study site, BMI, abdominal circumference, smoking, diabetes mellitus, hypertension (presence or absence), systolic blood pressure, ECG evidence of LVH, **F**amily history of premature CAD, and plasma lipid parameters. Separate models will be created for each measure of renal function (urinary microalbumin, eGFR by MDRD, cystatin C)

4. We will assess if the optimal threshold levels for hs-cTnT and NT-proBNP differ across stages of renal function using ROC curves and reporting operating characteristics at various thresholds across renal function stages.

5. If β_2-microglobulin and β-trace protein are found to be predictive of cardiovascular outcomes in ARIC, we will perform exploratory analysis of correlation between these renal analytes and hs-cTnT and NT-proBNP similar to the manner described above for cystatin C.

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)?

MS #6 - (Sharrett et al. 1994)

MS #606 - (Folsom et al. 2002)

MS #889 - (Ballantyne et al. 2004)

MS #934 - (Folsom et al. 2006)

MS #940 - (Ballantyne et al. 2005)

MS #1172 - (Nambi et al. 2008)

MS # 952 - (Astor et al. 2006)

MS # 1118 - (Kottgen et al. 2007)

(Hsu et al. 2009)

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* _2008.10__)

___ 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

Al Suwaidi, J., D. Reddan, K. Williams, K. Pieper, R. Harrington, R. Califf, C. Granger, E. Ohman & D. J. Holmes (2002) Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. *Circulation,* 106**,** 974-80.

Apple, F., M. Murakami, L. Pearce & C. Herzog (2002) Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. *Circulation,* 106**,** 2941-5.

--- (2004) Multi-biomarker risk stratification of N-terminal pro-B-type natriuretic peptide, high-sensitivity C-reactive protein, and cardiac troponin T and I in end-stage renal disease for all-cause death. *Clin Chem,* 50**,** 2279-85.

Astor, B., J. Coresh, G. Heiss, D. Pettitt & M. Sarnak (2006) Kidney function and anemia as risk factors for coronary heart disease and mortality: the Atherosclerosis Risk in Communities (ARIC) Study. *Am Heart J,* 151**,** 492-500.

Aviles, R., A. Askari, B. Lindahl, L. Wallentin, G. Jia, E. Ohman, K. Mahaffey, L. Newby, R. Califf, M. Simoons, E. Topol, P. Berger & M. Lauer (2002) Troponin T levels in patients with acute coronary syndromes, with or without renal dysfunction. *N Engl J Med,* 346**,** 2047-52.

Ballantyne, C., R. Hoogeveen, H. Bang, J. Coresh, A. Folsom, L. Chambless, M. Myerson, K. Wu, A. Sharrett & E. Boerwinkle (2005) Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident ischemic stroke in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. *Arch Intern Med,* 165**,** 2479-84.

Ballantyne, C., R. Hoogeveen, H. Bang, J. Coresh, A. Folsom, G. Heiss & A. Sharrett (2004) Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study. *Circulation,* 109**,** 837-42.

Brantsma, A., S. Bakker, H. Hillege, D. de Zeeuw, P. de Jong & R. Gansevoort (2008) Cardiovascular and renal outcome in subjects with K/DOQI stage 1-3 chronic kidney disease: the importance of urinary albumin excretion. *Nephrol Dial Transplant,* 23**,** 3851-8.

de Lemos, J., D. Morrow, J. Bentley, T. Omland, M. Sabatine, C. McCabe, C. Hall, C. Cannon & E. Braunwald (2001) The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med,* 345**,** 1014-21.

Fliser, D. & E. Ritz (2001) Serum cystatin C concentration as a marker of renal dysfunction in the elderly. *Am J Kidney Dis,* 37**,** 79-83.

Folsom, A., N. Aleksic, D. Catellier, H. Juneja & K. Wu (2002) C-reactive protein and incident coronary heart disease in the Atherosclerosis Risk In Communities (ARIC) study. *Am Heart J,* 144**,** 233-8.

Folsom, A., L. Chambless, C. Ballantyne, J. Coresh, G. Heiss, K. Wu, E. Boerwinkle, T. J. Mosley, P. Sorlie, G. Diao & A. Sharrett (2006) An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: the atherosclerosis risk in communities study. *Arch Intern Med,* 166**,** 1368-73.

Hsu, C., F. Brancati, B. Astor, W. Kao, M. Steffes, A. Folsom & J. Coresh (2009) Blood pressure, atherosclerosis, and albuminuria in 10,113 participants in the atherosclerosis risk in communities study. *J Hypertens,* 27**,** 397-409.

Inoue, T., Y. Eguchi, T. Matsumoto, Y. Kijima, Y. Kato, Y. Ozaki, K. Waseda, H. Oda, K. Seiki, K. Node & Y. Urade (2008) Lipocalin-type prostaglandin D synthase is a powerful biomarker for severity of stable coronary artery disease. *Atherosclerosis,* 201**,** 385-91.

Keller, T., C. Messow, E. Lubos, V. Nicaud, P. Wild, H. Rupprecht, C. Bickel, S. Tzikas, D. Peetz, K. Lackner, L. Tiret, T. Münzel, S. Blankenberg & R. Schnabel (2009) Cystatin C and cardiovascular mortality in patients with coronary artery disease and normal or mildly reduced kidney function: results from the AtheroGene study. *Eur Heart J,* 30**,** 314-20.

Kistorp, C., I. Raymond, F. Pedersen, F. Gustafsson, J. Faber & P. Hildebrandt (2005) N-terminal pro-brain natriuretic peptide, C-reactive protein, and urinary albumin levels as predictors of mortality and cardiovascular events in older adults. *JAMA,* 293**,** 1609-16.

Kottgen, A., S. Russell, L. Loehr, C. Crainiceanu, W. Rosamond, P. Chang, L. Chambless & J. Coresh (2007) Reduced kidney function as a risk factor for incident heart failure: the atherosclerosis risk in communities (ARIC) study. *J Am Soc Nephrol,* 18**,** 1307-15.

Nambi, V., R. C. Hoogeveen, L. Chambless, Y. Hu, H. Bang, J. Coresh, H. Ni, E. Boerwinkle, T. Mosley, R. Sharrett, A. R. Folsom & C. M. Ballantyne (2008) Lipoprotein-Associated Phospholipase A2 and High-Sensitivity C-Reactive Protein Improve the Stratification of Ischemic Stroke Risk in the Atherosclerosis Risk in Communities (ARIC) Study. ***Stroke,*** STROKEAHA.107.513259.

Okuno, S., E. Ishimura, K. Kohno, Y. Fujino-Katoh, Y. Maeno, T. Yamakawa, M. Inaba & Y. Nishizawa (2009) Serum beta2-microglobulin level is a significant predictor of mortality in maintenance haemodialysis patients. *Nephrol Dial Transplant,* 24**,** 571-7.

Omland, T., A. Persson, L. Ng, R. O'Brien, T. Karlsson, J. Herlitz, M. Hartford & K. Caidahl (2002) N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. *Circulation,* 106**,** 2913-8.

Peacock, W. t., T. De Marco, G. Fonarow, D. Diercks, J. Wynne, F. Apple & A. Wu (2008) Cardiac troponin and outcome in acute heart failure. *N Engl J Med,* 358**,** 2117-26.

Priem, F., H. Althaus, M. Birnbaum, P. Sinha, H. Conradt & K. Jung (1999) Beta-trace protein in serum: a new marker of glomerular filtration rate in the creatinine-blind range. *Clin Chem,* 45**,** 567-8.

Reichlin, T., W. Hochholzer, S. Bassetti, S. Steuer, C. Stelzig, S. Hartwiger, S. Biedert, N. Schaub, C. Buerge, M. Potocki, M. Noveanu, T. Breidthardt, R. Twerenbold, K. Winkler, R. Bingisser & C. Mueller (2009) Early diagnosis of myocardial infarction with sensitive cardiac troponin assays. *N Engl J Med,* 361**,** 858-67.

Sharrett, A., W. Patsch, P. Sorlie, G. Heiss, M. Bond & C. Davis (1994) Associations of lipoprotein cholesterols, apolipoproteins A-I and B, and triglycerides with carotid atherosclerosis and coronary heart disease. The Atherosclerosis Risk in Communities (ARIC) Study. *Arterioscler Thromb,* 14**,** 1098-104.

Shlipak, M., R. Katz, M. Sarnak, L. Fried, A. Newman, C. Stehman-Breen, S. Seliger, B. Kestenbaum, B. Psaty, R. Tracy & D. Siscovick (2006) Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. *Ann Intern Med,* 145**,** 237-46.

Shlipak, M., M. Sarnak, R. Katz, L. Fried, S. Seliger, A. Newman, D. Siscovick & C. Stehman-Breen (2005) Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med,* 352**,** 2049-60.

Stevens, L., C. Schmid, T. Greene, L. Li, G. Beck, M. Joffe, M. Froissart, J. Kusek, Y. Zhang, J. Coresh & A. Levey (2009) Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int,* 75**,** 652-60.

Wu, A., A. Jaffe, F. Apple, R. Jesse, G. Francis, D. Morrow, L. Newby, J. Ravkilde, W. Tang, R. Christenson, C. Cannon & A. Storrow (2007) National Academy of Clinical Biochemistry laboratory medicine practice guidelines: use of cardiac troponin and B-type natriuretic peptide or N-terminal proB-type natriuretic peptide for etiologies other than acute coronary syndromes and heart failure. *Clin Chem,* 53**,** 2086-96.

Zethelius, B., L. Berglund, J. Sundström, E. Ingelsson, S. Basu, A. Larsson, P. Venge & J. Arnlöv (2008) Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *N Engl J Med,* 358**,** 2107-16.

Zumrutdal, A., S. Sezer, S. Demircan, G. Seydaoglu, F. Ozdemir & M. Haberal (2005) Cardiac troponin I and beta 2 microglobulin as risk factors for early-onset atherosclerosis in patients on haemodialysis. *Nephrology (Carlton),* 10**,** 453-8.