ARIC Manuscript Proposal #3770

PC Reviewed: 2/9/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: NT-proBNP as a Univariate Predictor of All-Cause Mortality in Elderly People in The Community

b. Abbreviated Title (Length 26 characters): NT-proBNP and Mortality

2. Writing Group:
Writing group members: Magnus Wijkman, Brian Claggett, Scott Solomon, Marc Pfeffer [others welcome].

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

First author: Magnus Wijkman
Address: Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115
Phone: (617) 860-8460
Fax: (617) 732-5291
E-mail: mwijkman@bwh.harvard.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: Scott Solomon
Address: Brigham & Women's Hospital, 75 Francis Street, Boston, MA 02115
Phone: 857-307-1960
E-mail: ssolomon@bwh.harvard.edu

3. Timeline:
Analysis to begin immediately, first draft April 2021

4. Rationale:

B-type natriuretic peptides are peptide hormones that are synthesized in and released from the ventricular myocytes in response to cardiac overload and ischemia [1,2]. Across a wide range of patient populations, circulating levels of the N-terminal fragment of its pro-hormone (NT-proBNP) have been shown to predict cardiovascular risk independently of traditional risk factors, and to add incremental value to multivariate prediction models [3,4,5,6,7]. In clinical trials populations selected for prior cardiovascular events and for chronic cardiovascular or renal disease, plasma levels of NT-proBNP have even been shown to predict cardiovascular events and death equally well as multivariate prediction models [8,9].

However, the discriminatory ability of NT-proBNP as a univariate predictor of mortality has not been compared with multivariate prediction models in population-based cohorts of elderly patients with and without prevalent cardiovascular disease and diabetes. Therefore, we propose to evaluate whether NT-proBNP, as a univariate predictor, has a discriminatory ability for all-cause mortality which is similar in magnitude as that of an established risk model (The Pooled Cohort Equation Model, previously used as the comparator model when evaluating other novel biomarkers in the ARIC cohort [10]). We furthermore propose to explore whether the predictive and discriminatory abilities of NT-proBNP varies by diabetes status, by cardiovascular disease history, and by length of follow-up. These analyses may help us understand better how NT-proBNP performs as a predictor of mortality in an unselected cohort of elderly persons.

5. Specific Study Questions:

- Is the discriminatory ability of NT-proBNP, as a univariate predictor, of a similar magnitude as the discriminatory abilities of multivariate risk models, for the prediction of all-cause mortality?

- Is the discriminatory ability of NT-proBNP, as a univariate predictor, similar in patients with and without diabetes, and in patients with and without prior cardiovascular events, for the prediction of all-cause mortality?

- Does the discriminatory ability of NT-proBNP, as a univariate predictor, change with the length of follow-up, for the prediction of all-cause mortality?

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 observational cohort study

Inclusion criteria: ARIC participants with visit 5 data for NT-proBNP

Exclusion criteria:

- Missing data for variables in the risk prediction models

- Missing follow-up data for mortality
- Missing data for prior CVD status
- Race other than Black or White
- Black participants at Minneapolis and Washington

Outcomes: all-cause mortality

Model 1 = The Pooled Cohort Equation Model: age, sex, Black race, total cholesterol, HDL cholesterol, systolic blood pressure, use of antihypertensive medication, smoking status, and diabetes status

Model 2: same variables as in model 1, with addition of eGFR, hs-CRP and hs-TnT

Summary of data analysis: Baseline characteristics and mortality rates will be presented overall, by quartiles of NT-proBNP, by diabetes status, and by cardiovascular disease history. Prior cardiovascular disease history will be defined as MI/stroke/heart failure history at visit 1 and/or incident MI/stroke/heart failure between visit 1 and visit 5. Undetectable but non-missing values for NT-proBNP and hs-TNT will be assigned the values of 2.5 and of 0.003, respectively. Values of NT-proBNP will be log-transformed. Cox proportional hazards models and Harrel´s C-statistics with 95% confidence intervals will be used to assess the prognostic and discriminatory abilities separately for Model 1, for Model 2, for NT-proBNP as a univariate predictor, and for Model 2 with the addition of NT-proBNP.

Differences in C-statistics will be tested for statistical significance
- between NT-proBNP and Model 1
- between NT-proBNP and Model 2
- between NT-proBNP and the full model

The primary research question will be explored also in the following pre-specified sub-groups:
- with/without diabetes
- with/without cardiovascular disease history

The primary research question will also be explored in a sensitivity analysis:
- follow-up period restricted to two years
- follow-up period restricted to four years

Anticipated methodologic limitations or challenges:

This analysis will assess the prognostic information of NT-proBNP measured on one single occasion (visit 5) and will not take into account possible changes in NT-proBNP during follow-up.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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/mantrack/maintain/search/dtSearch.html

___X___ Yes _____ No

10. What are the most related manuscript proposal in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

Most related publications:

Oluleye OW, Folsom AR, Nambi V, Lutsey PL, Ballantyne CM. Troponin T, B-type natriuretic peptide, C-reactive protein, and cause-specific mortality. Ann Epidemiol 2013;23:66-73.

Gori M, Gupta DK, Claggett B, et al. Natriuretic Peptide and High-Sensitivity Troponin for Cardiovascular Risk Prediction in Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study. Diabetes Care 2016;39:677-85.

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

11.b. If yes, is the proposal
___ A. primarily the result of an ancillary study (list number* _____)
___ 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 https://sites.cscc.unc.edu/aric/approved-ancillary-studies

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.

References

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2. Sabatine MS, Morrow DA, de Lemos JA, et al. Acute changes in circulating natriuretic peptide levels in relation to myocardial ischemia. J Am Coll Cardiol 2004;44:1988-95.

3. Omland T, Sabatine MS, Jablonski KA, et al. Prognostic value of B-Type natriuretic peptides in patients with stable coronary artery disease: the PEACE Trial. J Am Coll Cardiol 2007;50:205-14.

4. Paget V, Legedz L, Gaudebout N, et al. N-terminal pro-brain natriuretic peptide: a powerful predictor of mortality in hypertension. Hypertension 2011;57:702-9.

5. McMurray JJ, Uno H, Jarolim P, et al. Predictors of fatal and nonfatal cardiovascular events in patients with type 2 diabetes mellitus, chronic kidney disease, and anemia: an analysis of the Trial to Reduce cardiovascular Events with Aranesp (darbepoetin-alfa) Therapy (TREAT). Am Heart J 2011;162:748-55 e3.

6. Gori M, Gupta DK, Claggett B, et al. Natriuretic Peptide and High-Sensitivity Troponin for Cardiovascular Risk Prediction in Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study. Diabetes Care 2016;39:677-85.

7. Oluleye OW, Folsom AR, Nambi V, Lutsey PL, Ballantyne CM, Investigators AS. Troponin T, B-type natriuretic peptide, C-reactive protein, and cause-specific mortality. Ann Epidemiol 2013;23:66-73.

8. Wolsk E, Claggett B, Pfeffer MA, et al. Role of B-Type Natriuretic Peptide and N-Terminal Prohormone BNP as Predictors of Cardiovascular Morbidity and Mortality in Patients With a Recent Coronary Event and Type 2 Diabetes Mellitus. J Am Heart Assoc 2017;6.

9. Malachias MVB, Jhund PS, Claggett BL, et al. NT-proBNP by Itself Predicts Death and Cardiovascular Events in High-Risk Patients With Type 2 Diabetes Mellitus. J Am Heart Assoc 2020:e017462.

10. Jia X, Sun W, Hoogeveen RC, et al. High-Sensitivity Troponin I and Incident Coronary Events, Stroke, Heart Failure Hospitalization, and Mortality in the ARIC Study. Circulation 2019;139:2642-53.