

ARIC Manuscript Proposal #1959

PC Reviewed: 7/10/12
SC Reviewed: _____

Status: A
Status: _____

Priority: 2
Priority: _____

1.a. Full Title: Troponin T, NT-proBNP and venous thromboembolism

b. Abbreviated Title (Length 26 characters): TnT, NT-proBNP and VTE

2. Writing Group:

Writing group members: Aaron Folsom, Pam Lutsey, Vijay Nambi, Christopher DeFilippi, Susan Heckbert, Mary Cushman, Christie Ballantyne

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

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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).

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3. Timeline: Finish by summer 2012

4. Rationale:

HS-TnT and NT-proBNP have been shown in ARIC and CHS to be important biomarkers for CHD and HF risk. There are no data on these biomarkers and risk for venous

thromboembolism (DVT and PE). We will address this in LITE, which includes both the ARIC and CHS cohorts.

Generally NT-proBNP is a marker of volume overload and TnT is considered a marker of ischemic cardiac myo-necrosis. Volume overload could contribute to VTE risk, via increased stasis and thrombogenesis. Heart failure is, itself, a known acute risk factor for VTE by these mechanisms. The rationale for TnT and VTE is less clear, as CHD is generally not felt to be a VTE risk factor, but should be explored. Indirect mechanisms, such as vascular inflammation or general “cardiac stress”, linking these markers with VTE are plausible. However, it is also possible that these two markers would not reflect any causal process, but would rather be markers of general VTE risk or the result of uncontrolled confounding.

5. Main Hypothesis/Study Questions:

TnT and NT-proBNP are independently and positively associated with VTE occurrence.

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

- A cohort analysis of participants who attended ARIC visit 4. (We will also include CHS in a similar fashion.)

Exclusion

-Participants with missing data for hs-cTnT, NT-proBNP at visit 4; who report a race other than Caucasian or African American; who had a VTE prior to visit 4; or who reported taking anticoagulants at visit 4. We are discussing still whether to exclude prevalent HF or CHD, in order to look at these biomarkers in the absence of diagnosed clinical heart disease.

Exposure

Hs-cTnT, NT-proBNP measured from plasma samples during ARIC visit 4

Outcome

-Incident VTE after visit 4 (n=227). (In CHS there are n= 200 VTEs)

Other variables (confounders, mediators, or potential effect modifiers)

-VTE risk factors identified in other LITE reports, including age, race, sex, BMI, diabetes, HRT, CRP, eGFR, FVIII, von Willebrand factor (ARIC only), aPTT (ARIC only), etc.

Statistical analysis

Analyses initially will be done study specific (ARIC/CHS) and a test for interaction by study or age tested. Results for the two studies may be pooled if they look homogeneous.

Hs-cTnT will be modeled as both a continuous and as a categorical variable reported in categories from undetectable levels to $\geq 0.014\mu\text{g/L}$. NT-proBNP will also be modeled as both continuous and categorical variable reported in quintiles. Splines will be examined to better understand the continuous relations.

Cox proportional hazards regression will be used to determine the hazard ratios of incident VTE by hs-cTnT or NT-proBNP. Age, gender and race will be adjusted for as confounders in a minimally adjusted model 1. In the 2nd model, other covariates will be adjusted for. We will also run models considering both markers together, to test for statistical synergy, in relation to VTE incidence. This might involve Kaplan-Meier analysis of hi/low values of each. In addition to total VTE, we will also examine provoked and unprovoked VTE as subsets.

If NT-proBNP is related to VTE, we may have to explore whether HF itself is a risk factor.w

7.a. Will the data be used for non-CVD analysis in this manuscript? ___ Yes
__xx__ 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
__xx__ 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.cscce.unc.edu/ARIC/search.php>

__xx__ 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)?

1811: Association of high sensitive Troponin T (hs-cTnT),N- Terminal pro- brain natriuretic peptide (NT-proBNP) and high sensitivity C- reactive protein (hs-CRP) with cause- specific mortality: ARIC study

1563: Saunders et al. Cardiac Troponin T Measured by a Highly Sensitive Assay Predicts Coronary Heart...*Circulation*.2011; 123: 1367-1376

