

## ARIC Manuscript Proposal #2072

PC Reviewed: 2/12/13  
SC Reviewed: \_\_\_\_\_

Status: A  
Status: \_\_\_\_\_

Priority: 2  
Priority: \_\_\_\_\_

**1.a. Full Title:** Orthostatic Hypotension and Risk of Venous Thromboembolism

**b. Abbreviated Title (Length 26 characters):** Orthostatic Htn & VTE

**2. Writing Group:**

Writing group members: Liz Bell, Sunil Agarwal, Pam Lutsey, Mary Cushman, Susan Heckbert, Aaron Folsom

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

**First author: Liz Bell**

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**3. Timeline:** hope to finish by summer 2013.

**4. Rationale:**

Venous thromboembolism risk is related to physical characteristics that affect venous return. For example, people with longer legs or increased calf circumference are at increased risk of VTE.

Although Virchow postulated a role for venous flow in the etiology of VTE, other than a role for immobility, little is known about venous function and VTE risk. The venous system of the legs is a large capacitance system, and upon standing from supine position, blood pools (1). This results in a decrease in venous return to the heart or a decrease in cardiac output. To maintain cardiac output there is immediate parasympathetic withdrawal, followed by sympathetic activation to increase heart rate first, and then to increase peripheral resistance. In individuals with a healthy venous system and skeletal muscle mass, venous return increases with time too. Those with an inability to equilibrate and maintain blood pressure manifest as orthostatic hypotension. In this case, there is an increased duration of venous pooling (1). Thus, a logical hypothesis is that increased

duration of venous pooling associated with orthostatic hypotension may increase the risk of venous thrombosis.

A note of caution: In a reverse causal direction, VTE, itself, may cause insufficiency in venous values, which may cause or contribute to postural hypotension. Thus, OH could simply be a marker of poor venous return.

No prior publication on orthostatic hypotension and VTE risk has been found.

## **5. Main Hypothesis/Study Questions:**

Orthostatic hypotension is associated with VTE risk in ARIC.

CHS has orthostatic BP at Years 2 and 5 and our intent is to include both studies in this paper.

## **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 group: ARIC baseline. Exclude those with prior VTE history or on anticoagulation.

Events: incident VTEs after baseline

Exposure: orthostatic hypotension assessed at visit 1.

At the baseline examination, after 20 minutes of resting in the supine position, blood pressure was measured approximately every 30 seconds for 2 min (2–5 measurements, 90% had  $\geq 4$  measurements) using Dinamap 1846 SX, automated oscillometric device. Participants were then asked to stand, and BP measurements were repeated during the first 2 min after standing (2–5 measurements, 91% had  $\geq 4$  measurements). BP change was defined as the difference between the average standing and average supine after excluding the 1st standing measurement, as BP homeostasis occurs during the first 30 s after standing. Postural hypotension was defined as a systolic blood pressure (SBP) drop  $\geq 20$  mmHg or diastolic blood pressure (DBP)  $\geq 10$  mmHg from supine to standing.

Main analysis: time to event, as in other ARIC VTE papers. The relation of covariates and orthostatic hypotension will be examined before multivariate modeling.

Covariates:

Most likely confounders: age, race, sex, BMI, diabetes, smoking, hypertension, systolic blood pressure, eGFR, medications potentially affecting BP or orthostatic BP.

Unlikely to confound because not expected to be related to exposure and/or outcome, but worth verifying: factor VIII, von Willebrand factor, aPTT, baseline CVD, and serum albumin, leg length.

Potential mediators if we see an association: possibly factor VIII, von Willebrand factor, aPTT, but causal role not clear.

## Reference

1. Smit AAJ, et al. Pathophysiological basis of orthostatic hypotension in autonomic failure. J Physiol 1999;519.1:1-10.

**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 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?**

\_\_xx\_\_ Yes    \_\_\_ 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"?**

\_\_xx\_\_ 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.csc.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)?**

None.

**11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?**    \_\_xx\_\_ Yes    \_\_\_ No

**11.b. If yes, is the proposal**

  xx   **A. primarily the result of an ancillary study (list number\* \_2006.16\_)**

       **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.csc.unc.edu/aric/forms/>