ARIC Manuscript Proposal # 1170

PC Reviewed: 06_/_20_/06	**Status: _A_**	**Priority: _2_**
SC Reviewed: _06/23/06_	**Status: _A_**	**Priority: _2_**

1.a. Full Title: Reproductive Factors, Hormone Replacement, and Venous Thromboembolism

b. Abbreviated Title (Length 26 characters): Reproductive Factors and VTE

2. Writing Group:
Writing group members: Aaron Folsom, Mary Cushman, Richard White, Wayne Rosamond, Susan Heckbert

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

F**irst author**: Aaron R. Folsom, MD

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Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author):
Address:

Phone: Fax:
E-mail:

3. Timeline: Complete in 2006.

4. Rationale: HRT has clearly been shown in clinical trials, such as HERS and WHI, to increase risk of VTE. We have not yet reported on the HRT association in LITE or interacting factors.

A recent case-control study indicated that markers of lifetime endogenous estrogen exposure may affect VTE risk (1). Specifically, VTE risk was associated positively with age at menopause and number of children. We wish to replicate this in LITE and consider possible mediating factors.

5. Main Hypothesis/Study Questions:

VTE risk is associated

- Positively with age at menopause
- Positively with parity
- Positively with HRT use (estrogen alone, estrogen plus progestin) and there are synergistic interactions with other VTE risk factors (eg, age, BMI, factor VIII, D-dimer, gene variants)

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).

Design: LITE (longitudinal cohort of ARIC and CHS).

Exclusions: Baseline warfarin, "no DNA use" for DNA variables, men

Dependent: VTE occurrence.

Independent: Menopause status (ARIC), age at menopause, oophorectomy/hysterectomy statuses and ages, gravidity, parity, HRT. For the most part, reproductive variables are static during follow-up, except for a proportion of ARIC women who undergo menopause or related surgery. Only oral HRT will be examined. HRT analysis is complicated by varying intervals of inquiry for ARIC versus CHS, various combinations, etc. Time dependent exposures will be needed.

Analysis: Proportional hazards regression is the primary method. Interactions will be tested by stratification and modeling. Analyses are also done by study (ARIC, CHS); primary or secondary VTE; incident or recurrent VTE; and subgroups based on other covariates.

Covariates: Age, race, study, BMI, diabetes, factor VIII. In a nested case-control subset we have D-dimer, factor V Leiden, and prothrombin G20210A. Thus, these covariates can only be analyzed in the subset using logistic regression.

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 ICTDER02 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 ICTDER02 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? __X__ 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 ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
__X__ 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)?

None.

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* 1998.03**)**
_____ 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

1. Simon T, Beau Yon de Jonage-Canonico M, Oger E, Wahl D, Conard J, Meyer G, Emmerich J, Barrellier MT, Guiraud A, Scarabin PY; EStrogen and THromboEmbolism Risk (ESTHER) Study Group. Indicators of lifetime

endogenous estrogen exposure and risk of venous thromboembolism. *J Thromb Haemost* 2006;4:71-76.