ARIC Manuscript Proposal Form

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Publication Committee Review Date:
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ARIC Manuscript Proposal Number: # **4380**

1.a. Full Title: Frailty and Risk of Venous Thromboembolism in Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study

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

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:
Writing group members: Tobyn S Chiu, Pamela L Lutsey, Mary Cushman, Weihong Tang, Jim Pankow, Yejin Mok, Anna M Kucharska-Newton and Gwen B Windham

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __PENDING___ **[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 (The ARIC author should be involved enough in ARIC to be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

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3. Timeline: Analysis and manuscript draft will be completed in 10 months

4. Rationale:

Venous thromboembolism (VTE) is a serious disease that affects up to 1 million Americans each year, and is more common at older ages.[1,2] It consists of both deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE has an overall 1-year mortality rate of 20-25%.[3,4] Therefore, there is a need to identify risk factors to target for effective prevention. This is especially true for older adults, who have the high incidence rates.

Both VTE and frailty occur more frequently in older adults.[2,5] In a prior cross-sectional analysis of ARIC data, participants (mean age 75 years) with a history of VTE had 3.81 times the odds of frailty compared with those who did not have any history of VTE, after adjustment for demographics.[6] The Age and Thrombosis-Acquired and Genetic risk factors in the Elderly Study, which has a case-control design, also reported a 2.9 times greater odds of VTE (OR = 2.9, 95% CI = 1.6-5.3) in individuals with impairment in two or more activities of daily living,[7] The Cardiovascular Health Study (CHS) is the only prospective cohort we are aware of that has evaluated the association between frailty and incident VTE in a non-clinical sample[8] In this paper by Folsom et al., the authors reported a higher risk of VTE in people who were frail compared with those that had no frailty [RR (95% CI) =1.31 (0.93-1.84)].[8] As evidenced by the confidence intervals, precision was poor (n participants who were frail and developed VTE = 9).[8] Also, the authors did not evaluate VTE risk according to components of the frailty score. Some other studies have examined frailty and VTE risk in clinical populations. For instance, a meta-analysis including nine cohort studies found that, in patients with hip fracture, those who were frail at admission for surgery had a higher incidence of postoperative VTE.[9]

Some individual components of commonly used frailty scores have been evaluated in relation to incident VTE in previous studies. Low physical activity is considered a component of the phenotypic frailty syndrome that may contribute to VTE risk through stasis, activation of coagulation and inflammatory pathways.[2,10] Numerous studies have examined the association between physical activity and VTE to find that, compared to low physical activity, high physical activity is associated with lower VTE risk.[11] The previously mentioned Age and Thrombosis-Acquired and Genetic risk factors in the Elderly Study case-control study evaluated individual components of their activities of daily living score, some of which were similar to those in ARIC's frailty metric, with VTE risk. They found VTE risk was three times as great (OR = 3.0, 95% CI = 1.9-4.7) in those with impaired mobility, four times as great (OR = 4.0, 95% CI = 2.5-6.3) in those with a sedentary life style, and 2.3 times as great (OR = 2.3, 95% CI = 1.5-3.4) in those with weak handgrip strength.[7] The Tromsø cohort also recently reported that weak hand grip strength was associated with an elevated risk of VTE.[12]

A need exists to better understand the relationship between frailty and VTE to allow for development of strategies that would decrease VTE in older adults.[13] Using data from the ARIC study, which has a larger sample size and higher frailty and incident VTE counts than the CHS, this proposed study will examine the relationship between frailty and its individual components and risk of incident VTE. In addition to VTE overall, we will evaluate the associations with provoked and unprovoked VTE.

5. Main Hypothesis/Study Aims:

Aim 1: Study the association between frailty and incident VTE.

Hypothesis: Participants who are frail will be at greater risk of VTE than those who are robust. Pre-frail participants will have intermediate risk. Associations will exist for VTE overall, for unprovoked cases and for provoked cases.

Aim 2: Evaluate the association between individual components of the frailty score and risk of incident VTE.

Hypothesis: Poorer levels of the individual components of the frailty score will be associated with greater risk of VTE. Associations will exist for VTE overall, for unprovoked cases and for provoked cases.

6. Design and analysis - please address the following aspects:

a) inclusion/exclusion
b) study design
c) outcome and other variables of interest with specific reference to the time of their collection
d) summary of data analysis
e) Any anticipated methodologic limitations or challenges if present

Study design: Prospective observational study using frailty ascertainment at ARIC visit 5 as baseline with VTE data post visit 5.

Inclusion criteria: ARIC participants who attended ARIC study visit 5 with frailty data at visit 5.

Exclusion criteria:

- Missing frailty data
- Prevalent VTE
- Missing covariate data
- Typical ARIC race-center exclusions (i.e., participants who do not identify as Black or white, and Black participants from the MN and MD centers).
- Anticoagulant medication use
    - We will also explore excluding participants with anticoagulant medication use at visit 5. Final decisions will be made after seeing the prevalence.

Exposure:

- Frailty has previously been operationalized in ARIC using the Fried frailty definition that was originally implemented in the CHS. [5,14] We will use the same definition as in the prior ARIC work.[14]
    - Robust=0 components, prefrail=1-2 components, frail=≥3 components
- Components of frailty ascertained at visit 5, as has been used previously in ARIC.
    - Weight loss
    - Low grip strength
    - Exhaustion
    - Slow walking speed
    - Low physical activity

Outcomes:

- Incident VTE after visit 5. VTE events have been previously adjudicated by medical record review and classified as provoked or unprovoked, with provoked cases being those secondary to underlying conditions including cancer, hospitalization, surgery, and major trauma.[15]

Covariates:
Age, sex, race, center, smoking status, BMI, and hs-CRP

In exploratory analyses we will also evaluate whether comorbid clinical conditions are also confounders (e.g. diabetes, hypertension, heart failure, chronic lung disease).

Statistical Analysis:
Descriptive statistics will be tabulated, stratified by frailty status. Cox proportional hazards regression modeling will be used to assess risk of incident VTE. The proportional hazards assumption will be tested by evaluating interactions with log time.

Aim 1:
Primary analysis: Evaluate the longitudinal association of frailty status with risk of incident VTE overall through 2020 or latest available data. Person-time will accrue from the visit 5 date until incident VTE, loss to follow up, death, or administrative censoring on December 31st, 2020.

Secondary analysis: We will also evaluate associations with risk of incident provoked and unprovoked VTE, respectively. We will censor if participants experience the other VTE event type than being analyzed (e.g., when analyzing unprovoked VTE we will censor at incident provoked VTE).

Cox proportional hazards regression modelling will be used with frailty as an ordinal variable (robust, prefrail, or frail).

Model 1: Adjust for age, sex, and race/center
Model 2: Additionally adjust for smoking, and BMI.
Model 3: Additionally adjust for hs-CRP

Aim 2:

Analyses described in Aim 1 will be repeated, with the exposure being individual frailty components.

Interactions
For both aims, we will evaluate interactions by age category (<75 yrs vs. ≥75 yrs) and sex.

f) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) . ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☐ Yes ☒ 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 is distributed to ARIC PIs annually, 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 ☒ 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 or the "sponsoring" ARIC 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website□Publications□Proposal Search]

☒ 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)?
3212 (Lutsey) Long-term consequences of VTE on physical functioning and quality of life
3238 (Mok) Clinically recognized varicose veins and physical function in older individuals
2338 (Mahmoodi) Association of traditional cardiovascular risk factors with venous thromboembolism: meta-analysis of community-based prospective cohorts
3372 (French) Weight change and risk of venous thromboembolism over 9 years in the ARIC cohort

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☒ **Yes** ☐ **No → Skip to question 12**

11.b. If yes to 11.a., is the proposal

☒ **A. primarily the result of an ancillary study**

☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

11.c. If yes to 11.a., list number* 2001.16 LITE; 2008.06 ARIC NCS for V6 function/TMW

*ancillary studies are listed by number
https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website Ancillary Studies 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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website Publications Publication Policies, Forms, and Guidelines].
http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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