September 14, 2016

ARIC Publications Committee:

Re: Conditional approval of MS Proposal #2809: “Venous thromboembolism and atrial fibrillation: Evidence of bi-directionality from the Atherosclerosis Risk in Communities (ARIC) Study.”

Dear ARIC Publications Committee,

Thank you for your thoughtful critique of our proposal. Below we respond to concerns in a point-point manner. Clean and track-changes versions of the proposal are also provided. We hope that we have adequately addressed your concerns.

The primary concern related to the limitation of the quality and timing of the data:

“We can see the interest in the hypothesis but we are concerned that the quality of the timing data could be a major limitation. We assume the limitations will note that the association could be partly due to increased surveillance for the other diagnosis (e.g. for AF after VTE diagnosis). It may be useful to analyze the data with and without (the proposal notes that AF detected in the same hospitalization as VTE will be censored) diagnoses within certain lag times of each other (e.g. same hospitalization, 30 days, 6 months). We also noted that the timing of the events, in particular AF is uncertain which is a limitation for this study. Someone may have had AF for years before it is detected at a visit or in a hospitalization.”

Response: Thank you for highlighting this limitation. We are cognizant of this limitation, but did not explicitly mention it in the proposal. The sensitivity analyses you have suggested are helpful. We have now included a new section in the proposal: “Methodological Considerations and Resultant Sensitivity Analyses” where we describe this limitation, and our plans to conduct the sensitivity analyses you noted above.

The second concern raised was in relation to the analysis censoring date:

“We were also puzzled as to why the end of study will be 2011 when we will soon have data to 2014.”

Response: Under the present LITE IV funding, VTE cases have been validated through the end of 2011. Given that only about half of VTE ICD codes are deemed events upon validation, we believe it is important to include only validated events in this analysis. We have added to the proposal a brief rationale for ending follow-up in 2011. Validation of cases through 2015 was proposed as part of LITE V. If additional cases are validated prior to publication of this manuscript, we will include them.
A third concern was related to an exploratory analysis; risk within the first 6 months after an event.

“It is also unclear how the time dependent analysis will address the issue of risk within the first 6 months after an event noted in the hypotheses.”

*Response:* We have removed this analysis, since (as noted in the original proposal) it was exploratory, and likely underpowered.

The final inquiry related to the use of CMS data, and whether our response to question #13 should be “yes”. We do not plan to use any CMS data in this analysis, therefore checking “no” is appropriate.

Please feel free to contact me with any further questions or suggestions.

Sincerely,
Pamela Lutsey
1.a. **Full Title**: Venous thromboembolism and atrial fibrillation: Evidence of bi-directionality from the Atherosclerosis Risk in Communities (ARIC) Study

b. **Abbreviated Title (Length 26 characters)**: VTE and AF: Bi-directionality

2. **Writing Group**:
   Writing group members: Pamela L Lutsey, Alvaro Alonso, Mary Cushman, Lin Y Chen, Erin D. Michos, Aaron R. Folsom, other interested Investigators welcome.

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

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**Name**: Aaron R Folsom  
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**Phone**: (612) 626-8862  
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**E-mail**:


4. **Rationale**:
   Atrial fibrillation (AF) and venous thromboembolism (VTE) are common conditions, particularly among the elderly. The lifetime risk for AF is 1 in 4, while the lifetime risk for VTE is 1 in 8 for persons at ~40 years of age. Both AF and VTE are associated with substantial morbidity and mortality, thus necessitating further investigation of predisposing factors. Recently it has been suggested that there may be a bidirectional association between AF and VTE, though these hypotheses require additional verification.
Conventionally deep vein thrombosis (DVT) and pulmonary embolism (PE) have been viewed as different clinical manifestations of the same disease. According to clinical dogma, thrombi typically originate in the deep veins (often of the legs); sometimes a thrombus breaks free and travels through the right side of the heart and into the pulmonary vasculature where it becomes a PE. However, it has been noted relatively recently that among PE patients, about half have no evidence of DVT by compression ultrasonography\(^4\)-\(^6\) or advanced magnetic resonance imaging,\(^7\) thus suggesting that pulmonary emboli may arise from sites other than the deep veins. It is well-established that atrial fibrillation is associated with thrombus formation in the left atrium, which can lead to ischemic stroke.\(^1\) Less is known about whether clot formation also occurs in the right atrium (i.e. right-side intracardiac thrombosis) of AF patients, though small clinical studies are supportive of an association.\(^8\),\(^9\) Recently the Tromsø study reported that the risk of VTE was elevated in atrial fibrillation patients.\(^10\) This association was particularly strong in the first 6 months after AF diagnosis, and was stronger for PE events than for DVT events. These findings are consistent with those from a prospective analysis of the Longitudinal Health Insurance Database 2000,\(^11\) and two case-control studies.\(^12\),\(^13\)

Conversely, small clinical studies have shown that PEs can lead to AF. PE increases pulmonary vascular resistance and right ventricular afterload by obstructing pulmonary arteries and triggering the release of vasoconstrictive mediators.\(^14\),\(^15\) Resultant increased right atrial pressure and strain may trigger AF. PE was independently associated with AF risk in the Tromsø study.\(^16\)

In sum, a bi-directional relation may be present between AF and VTE. However, the associations may not be causal but rather due to the coincidence of two chronic conditions in patients with poor health. Further work is needed to evaluate these associations.

5. Main Hypothesis/Study Questions:

Hypothesis #1: Individuals with incident AF are at elevated risk of developing VTE.
- Associations will be stronger for PE than for DVT.

Hypothesis #2: Individuals with incident VTE are at elevated risk of developing AF.
- Associations will be stronger for PE than for DVT.

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 cohort from baseline through 2011. 2011 was selected as the end date, as presently VTE cases have only been validated through 2011. If additional VTE cases are validated, we will extend follow-up, accordingly.

Inclusion/exclusion:
For all analyses, we will exclude individuals with prevalent AF or VTE, those who are not black or white, and blacks from Minnesota and Maryland.

Outcome:
- Hypothesis #1: VTE
The primary analysis will be for total VTE. Secondary analyses will explore as outcomes, separately, PE (including PE + DVT) and leg DVT. Individuals who experienced a non-leg DVT and no PE will not be counted as having VTE for this analysis.

-Hypothesis #2: AF

Other variables of interest:

Age, sex, race, physical activity, waist circumference, diabetes, smoking, height, systolic blood pressure, use of antihypertensive medication, prevalent coronary heart disease, prevalent heart failure, eGFR and anticoagulant use. In general, covariate information will come from the clinic visit preceding development of AF (for VTE incidence analyses) or VTE (for AF incidence analyses). Anticoagulant information will come from the annual follow-up phone calls. We will also consider using AFU information on self-reported diabetes and hypertension.

Summary of data analysis:

Characteristics of the entire ARIC study sample at visit 1 will be reported. Cox proportional hazards regression will be used for the primary analyses, and follow-up will begin at the visit 1 date.

Hypothesis #1: Individuals with incident AF are at elevated risk of developing VTE.

Person-time will accrue from ARIC baseline until the date of the incident VTE event, death, loss-to-follow-up, or December 31, 2011 (end of study). In instances when VTE and AF first appeared in the same hospital visit, we will censor on the day prior to the discharge date (i.e. neither the VTE nor the AF event will be counted in the analysis).

AF status will be included in all models as a time-dependent covariate. A series of nested models will be used:

- Model 1 will adjust for age, sex and race-site (5-level variable).
- Model 2 will further adjust for physical activity, waist circumference, diabetes, smoking, height, systolic blood pressure, use of antihypertensive medication, prevalent coronary heart disease, prevalent heart failure, eGFR.

In secondary analyses we will:

- Adjust for anticoagulant use as a time-dependent variable
- Consider as outcomes PE and DVT-only

Hypothesis #2: Individuals with incident VTE are at elevated risk of developing AF.

Person-time will accrue from ARIC baseline until the date of the incident AF event, death, loss-to-follow-up, or December 31, 2011 (end of study). In instances when VTE and AF first appeared in the same hospital visit, we will censor on the day prior to the discharge date (i.e. neither the VTE nor the AF event will be counted in the analysis).

VTE status will be included in all models as a time-dependent covariate. A series of nested models will be used:

- Model 1 will adjust for age, sex and race-site (5-level variable).
- Model 2 will further adjust for waist circumference, diabetes, smoking, height, systolic blood pressure, use of antihypertensive medication, prevalent coronary heart disease, prevalent heart failure, eGFR.

In secondary analyses we will:
- Consider PE and DVT-only as separate time-dependent exposures
- Adjust for anticoagulant use as a time-dependent variable

Interactions by age, race, sex and waist circumference will be evaluated by including cross-product terms in the models. Stratified results will be reported, as appropriate. The proportional hazards assumption will be tested.

Methodological Considerations and Resultant Sensitivity Analyses
An important potential limitation of this analysis relates to the quality of the timing data. In particular, the date of AF diagnosis may not be the true AF incidence date (date when AF developed), since AF is often undiagnosed. It is possible that if we observe an association between VTE and AF, that the association could be due to increased surveillance for other diseases (such as AF). To evaluate this possibility, we will conduct sensitivity analyses to explore inclusion AF and VTE diagnosed in the same hospitalization, and with various lags (e.g. requiring 30 days, 3 month or 6 months between diagnoses). We are cognizant of this important limitation, and will highlight it in the final manuscript.

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 ICTDER03 must be used to exclude persons with a value RES_OTHER = “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.)

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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)?

Several papers have evaluated CVD risk factors in relation to VTE risk. However, prior papers have not restricted to those with existing clinical conditions (e.g. VTE, AF).
11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __X__ Yes  ____ No

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   _X__  A. primarily the result of an ancillary study (list number* _2006.16____)
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13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript _____ Yes _____ No.

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

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4. Rationale:
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In sum, a bi-directional relation may be present between AF and VTE. However, the associations may not be causal but rather due to the coincidence of two chronic conditions in patients with poor health. Further work is needed to evaluate these associations.

5. Main Hypothesis/Study Questions:

Hypothesis #1: Individuals with incident AF are at elevated risk of developing VTE. This is particularly true during the first 6 months after an AF diagnosis. Associations will be stronger for PE than for DVT.

Hypothesis #2: Individuals with incident VTE are at elevated risk of developing AF. This is particularly true during the first 6 months after a VTE diagnosis. Associations will be stronger for PE than for DVT.

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).

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    analysis.
- Hypothesis #2: AF

Other variables of interest:
Age, sex, race, physical activity, waist circumference, diabetes, smoking, height, systolic
blood pressure, use of antihypertensive medication, prevalent coronary heart disease, prevalent
heart failure, eGFR and anticoagulant use. In general, covariate information will come from the
clinic visit preceding development of AF (for VTE incidence analyses) or VTE (for AF
incidence analyses). Anticoagulant information will come from the annual follow-up phone calls.
We will also consider using AFU information on self-reported diabetes and hypertension.

Summary of data analysis:
Characteristics of the entire ARIC study sample at visit 1 will be reported. Cox proportional
hazards regression will be used for the primary analyses, and follow-up will begin at the visit 1
date.

Hypothesis #1: Individuals with incident AF are at elevated risk of developing VTE.
  - Person-time will accrue from ARIC baseline until the date of the incident VTE event, death,
    loss-to-follow-up, or December 31, 2011 (end of study). In instances when VTE and AF first
    appeared in the same hospital visit, we will censor on the day prior to the discharge date (i.e.
    neither the VTE nor the AF event will be counted in the analysis).
  - AF status will be included in all models as a time-dependent covariate. A series of nested
    models will be used:
    - Model 1 will adjust for age, sex and race-site (5-level variable).
    - Model 2 will further adjust for physical activity, waist circumference, diabetes, smoking,
      height, systolic blood pressure, use of antihypertensive medication, prevalent coronary
      heart disease, prevalent heart failure, eGFR.
In secondary analyses we will:
- Adjust for anticoagulant use as a time-dependent variable
- Consider as outcomes PE and DVT-only

Hypothesis #2: Individuals with incident VTE are at elevated risk of developing AF.
  - Person-time will accrue from ARIC baseline until the date of the incident AF event, death,
    loss-to-follow-up, or December 31, 2011 (end of study). In instances when VTE and AF first
    appeared in the same hospital visit, we will censor on the day prior to the discharge date (i.e.
    neither the VTE nor the AF event will be counted in the analysis).
  - VTE status will be included in all models as a time-dependent covariate. A series of nested
    models will be used:
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In secondary analyses we will:
- Consider PE and DVT-only as separate time-dependent exposures
- Adjust for anticoagulant use as a time-dependent variable

Interactions by age, race, sex and waist circumference will be evaluated by including cross-product terms in the models. Stratified results will be reported, as appropriate. The proportional hazards assumption will be tested. In exploratory analyses we will evaluate whether the risk of VTE is highest in the first 6 months after an AF diagnosis. However, we will likely be underpowered for this analysis.

Methodological Considerations and Resultant Sensitivity Analyses

An important potential limitation of this analysis relates to the quality of the timing data. In particular, the date of AF diagnosis may not be the true AF incidence date (date when AF developed), since AF is often undiagnosed. It is possible that if we observe an association between VTE and AF, that the association could be due to increased surveillance for other diseases (such as AF). To evaluate this possibility, we will conduct sensitivity analyses to explore inclusion AF and VTE diagnosed in the same hospitalization, and with various lags (e.g., requiring 30 days, 3 month or 6 months between diagnoses). We are cognizant of this important limitation, and will highlight it in the final manuscript.

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Several papers have evaluated CVD risk factors in relation to VTE risk. However, prior papers have not restricted to those with existing clinical conditions (e.g. VTE, AF).

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*  _2006.16____) 

   ____    B. primarily based on ARIC data with ancillary data playing a minor role 

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References


