ARIC Manuscript Proposal Form

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Publication Committee Review Date: 5/13/2025 ARIC Manuscript Proposal Number#: 4672

1.a. Full Title: Incidence and Risk Factors for Aortic Dissection in a Healthy Community Populations: Findings from the Atherosclerosis Risk in Communities (ARIC) and Multi-Ethnic Study of Atherosclerosis (MESA) Studies

b. Abbreviated Title (Length 26 characters)

Aortic Dissection Risks

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ARIC sponsor to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located. The ARIC sponsor is responsible for **carefully reviewing the proposal and ensuring its soundness prior to submission to the ARIC Publications Committee.** (The ARIC sponsor 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:

- Late 2023: Ancillary study proposal submission, literature review, and approval
- Early – Mid 2024: Data acquisition, ICD code selection, outcome adjudication, and chart review
- Late 2024 – Mid 2025: Main proposal submission and data analysis
- Mid 2025 – Early 2026: Manuscript drafting, submission, revision, and publication

4. Rationale

Aortic dissection is a life-threatening condition resulting from a tear in the aortic wall, creating a false lumen that can compromise blood flow into vital organs. It is a rare disease with an incidence of 5 to 30 cases per 1 million people annually and it accounts for 3 out of every 1000 emergency visits.[1]

Based on the Stanford system, aortic dissection is classified as Type A or Type B, using the origin of the left subclavian artery as the reference point. Type A dissections involve the ascending aorta (proximal to the left subclavian artery), while Type B dissections originate distal to the left subclavian artery and do not involve the ascending aorta. Stanford type A is the most challenging to manage, and according to the International Registry of Acute Aortic Dissection, it carries an in-patient mortality of 22% while Stanford B, carries a mortality of 13%.[2]

Despite the high morbidity and mortality associated with aortic dissection, few studies provide epidemiological, population-based estimates using longitudinal data in people free of cardiovascular disease at baseline. Most studies rely on administrative databases limited to in-patient and regional data.[3–8] Consequently, these studies predominantly describe the clinical features, management, and outcomes of established aortic dissection cases, with less emphasis on in-depth analysis of risk factors. Additionally, risk factors in these studies are often assessed at the time of aortic dissection rather than years prior. One of such study using data from the International Registry of Acute Aortic Dissection (IRAD) indicated that a majority of patients with aortic dissection had a history of hypertension (77% overall), with a higher prevalence in those with type B acute aortic dissection (AAD) compared to type A AAD (81% vs. 74%).[9] Because risk factors like hypertension and smoking are often assessed only after aortic dissection in retrospective studies, their prevalence may be overestimated, potentially inflating the strength of their association with the condition.

To address these concerns, we plan to combine longitudinal data from ARIC and MESA to prospectively assess risk factors associated with aortic dissection in a general community

population, determine its incidence among individuals with these risk factors, and estimate the overall incidence of aortic dissection.

References:

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3. Harris D, Klyushnenkova E, Kalsi R, et al. Non-White Race is an Independent Risk Factor for Hospitalization for Aortic Dissection. Ethn Dis. 2016;26(3):363. doi:10.18865/ed.26.3.363.
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6. Mehta RH, O'Gara PT, Bossone E, et al. Acute type A aortic dissection in the elderly: clinical characteristics, management, and outcomes in the current era. J Am Coll Cardiol. 2002;40(4):685-692. doi:10.1016/s0735-1097(02)02005-3.
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8. Olsson C, Thelin S, Ståhle E, Ekbom A, Granath F. Thoracic aortic aneurysm and dissection: increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14,000 cases. Circulation. 2006;114(24):2611-2618. doi:10.1161/CIRCULATIONAHA.106.630400.
9. Pape LA, Awais M, Woznicki EM, et al. Presentation, Diagnosis, and Outcomes of Acute Aortic Dissection: 17-Year Trends From the International Registry of Acute Aortic Dissection. J Am Coll Cardiol. 2015;66(4):350-358. doi:10.1016/j.jacc.2015.05.029.

5. Main Hypothesis/Study Aims

1. To estimate the incidence of aortic dissection in the overall study population.
2. To estimate the incidence of aortic dissection stratified by risk factors.
3. To assess the risk factors associated with aortic dissection. We hypothesize that individuals who are Black, male, hypertensive, older, current smokers will have a stronger association with aortic dissection.
4. To develop a simple points-based risk scoring system that quantifies the contribution of specific risk factors to aortic dissection and can be used for clinical risk prediction, using results from our Cox proportional hazards models.

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

a) **Inclusion/exclusion:** Pooled individual level data from the MESA and ARIC cohort without prior history of aortic dissection.

b) **Study design:** Prospective observational multi-cohort study design

c) **Outcome and other variables of interest with specific reference to the time of their collection:**

Study Outcome

Incident aortic dissection

Outcome Ascertainment

Under our Ancillary Study, a thorough review of medical charts was conducted. To identify all cases of aortic dissection in the ARIC and MESA databanks, we utilized ICD-9 and ICD-10 codes to capture all potential instances of aortic aneurysms and dissections in order to maximize the identification of aortic dissection cases. Subsequently, we retrieved each patient's chart available through these ICD codes. Two physicians independently reviewed all available charts to confirm cases of aortic dissection, initially identifying 25 cases. Following this, ICD codes that yielded reliable confirmation of cases of aortic dissection were further used to extract additional cases from the databanks in participants where charts were not available for review, ultimately identifying a total of 97 cases of aortic dissection.

Covariates (measured at baseline in MESA and ARIC)

- Age (years): Measured in years.
- Sex: Defined as self-reported sex, categorized as either male or female.
- Race
- Education
- Body Mass Index (BMI): Calculated as a person's weight in kilograms divided by the square of their height in meters (kg/m^2), used to assess body fat and categorize weight status.
- Smoking Status: Individuals are categorized as current smokers if they have smoked cigarettes within the past 30 days, former smokers if they have smoked in the past but not in the last 30 days, and never smokers if they have never smoked cigarettes. For individuals who are former or current smokers, we will classify smoking history by pack years: those with fewer than 10 pack years as light smokers, 10 to 20 pack years as moderate smokers, and more than 20 pack years as heavy smokers.
- Dyslipidemia: Defined as the presence of any of the following: 1) total cholesterol (TC) >240 mg/dL; 2) triglycerides >200 mg/dL; 3) HDL cholesterol (HDL-C) <50 mg/dL for females or <40 mg/dL for males; 4) LDL cholesterol (LDL-C) >160 mg/dL; or 5) the use of lipid-lowering therapies.
- Diabetes: Physician diagnosis, use of insulin or an oral hypoglycemic agent, or a fasting glucose value ≥126 mg/dL at baseline examination.
- Hypertension: Defined as self-reported treatment for hypertension with one of six common classes of antihypertensive medications (thiazide diuretics, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin

type 2 receptor blockers, and others [α-blockers or peripheral vasodilators]) or a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg.

d) **Summary of data analysis:**

Baseline characteristics of participants, additionally stratified by aortic dissection status (yes/no), will be presented. These characteristics include age, sex, hypertension status (yes/no), systolic and diastolic blood pressure categories, BMI categories, smoking status (never, former, current), diabetes status (yes/no), and dyslipidemia status (yes/no). Continuous variables will be reported as mean ± standard deviation if they are normally distributed, and as median with interquartile range (IQR) if they are not. Categorical variables will be summarized by the number and the percentage across each category. Differences across categorical variables and age groups will be evaluated using Chi-Squared tests. For age, depending on its distribution, either an independent samples t-test will be applied if the data are normally distributed, or the Mann-Whitney U test will be used if they are not. This approach ensures a comprehensive analysis of how different sociodemographic (such as sex, race, education etc.) and cardiovascular factors might influence the incidence of aortic dissection across varied population segments.

Incidence rates, defined as the number of events per person-year, will be calculated using the total person-time at risk, summing the follow-up time of all individuals until the occurrence of aortic dissection, censoring, or the end of the study period. These rates will be stratified by hypertension, smoking, and diabetic status to examine differences in the occurrence of aortic dissection. This stratification will allow for the identification of potential variations in risk across different subgroups.

The associations between hypertension, current smoking, diabetes, dyslipidemia, and obesity (defined as BMI ≥30kg/m2) with the risk of aortic dissection will be examined using Cox proportional hazards models, adjusting for age, sex, and race. Subsequently, we will explore effect modification by age, sex, and race on the relationships between hypertension and current smoking and aortic dissection. This approach aims to determine whether these demographic factors modify the impact of hypertension and smoking on aortic dissection risk.

Additionally, in a supplementary analysis, we will assess the impact of smoking intensity among former and current smokers using pack years (categorized as <10, 10–20, and >20). We will perform subgroup analyses stratified by baseline cardiovascular disease (CVD) status to evaluate whether associations differ between individuals with and without prior CVD. We will further examine the effects of systolic blood pressure (SBP: <120, 120–129, 130–139, ≥140 mmHg) and diastolic blood pressure (DBP: <80, 80–89, ≥90 mmHg) categories on aortic dissection risk. These relationships will be analyzed using Cox proportional hazards models, adjusting for age, sex, race, diabetes, dyslipidemia, and hypertension as appropriate.

We will develop a simple additive model to quantify the risk of aortic dissection based on categorized risk factors. This approach will involve categorizing key risk factors, such as hypertension, current smoking, and diabetes, assigning a score to each category based on its associated risk. We will use Cox proportional hazards models to assess the impact of these risk

factors on aortic dissection risk, adjusting for age, sex, race, and dyslipidemia. Each risk factor will be given a specific point value, proportional to the hazard ratios derived from our analysis.

The risk scores will be additive, allowing us to evaluate how the risk of aortic dissection increases with the accumulation of risk factors. An individual's total risk score will be calculated by summing the points for each contributing factor, providing a straightforward assessment of their overall risk for aortic dissection. We will validate this scoring system by analyzing its predictive performance, including discrimination using the C-statistic and calibration through comparisons of predicted versus observed risks.

e) **Any anticipated methodologic limitations or challenges if present** No

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 PHF 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. Will the data be used by a for-profit organization in this manuscript? ☐ **Yes*** ☒ **No**

8. Will the DNA data be used in this manuscript? ☐ **Yes*** ☒ **No**

* Please carefully review the instructions and documentation on the ARIC website at: https://aric.cscc.unc.edu/aric9/researchers/Obtain_Submit_Data [ARIC website > Researchers > Obtain/Submit Data] for instructions on proper data use.

9. The lead author or the ARIC sponsor 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)?

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*

*ancillary studies are listed by number
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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.

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References: N/A

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