ARIC Manuscript Proposal Form

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Publication Committee Review Date: **08/13/24**
ARIC Manuscript Proposal Number: **#4518**

1.a. Full Title: Association of Cardiovascular Disease and Major Adverse Cardiovascular Events with Abdominal Aortic Aneurysm in the ARIC Study

b. Abbreviated Title (Length 26 characters): Association of MACE and AAA

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. AE **[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 writing to be performed August 2024 – October 2024

4. Rationale:

Abdominal aortic aneurysm (AAA) has been associated with significantly increased risk of adverse cardiovascular disease outcomes.[1] Most prominently, presence of AAA has been associated with significantly increased incidence of myocardial infarction (MI) and stroke.[2,3,4] For example, a retrospective registry-based study of over 40,000 participants in Denmark found that people who had previously undergone surgery to repair AAA had hazard ratios for MI and stroke of 2.1 and 1.8 respectively at a maximum of 20 years of follow-up, compared to the general population.[2]

People with AAA have been shown to experience significant excess mortality compared to the general population, and aortic diameter has been positively associated with both increased risk of cardiovascular mortality and incident CVD events.[4,5,6,7,8] A longitudinal population-based study of 6,640 participants in Norway, for example, reported an adjusted total mortality risk ratio of 3.73 at 10 years, and cardiovascular mortality risk ratio of 9.24, in people with an abdominal aortic diameter of 3-3.4cm compared to people with an aortic diameter of 2.1-2.3cm.[9] Among 4,734 participants in the Cardiovascular Health Study, an association was demonstrated between infrarenal aortic diameter and risk of incident CVD events including coronary heart disease, stroke, and congestive heart failure over a 10-year follow-up period.[7] Associations between AAA and MI, stroke, and excess mortality have therefore been established in existing literature for certain populations, particularly those comprised of disproportionately white, European subjects.

The composite endpoint of Major Adverse Cardiovascular Events (MACE) was originally codified by the FDA in 2008 for evaluation of cardiovascular outcomes of anti-hyperglycemic therapies.[10] In the context of observational studies, a three-point MACE outcome most commonly consists of acute MI, stroke, and all-cause death.[11] Recent epidemiologic studies of AAA have made use of this outcome measure, including one large study of AAA population screening data from the United Kingdom which estimated an adjusted hazard ratio for MACE of 1.79 among men with AAA compared to controls.[12] Elevated long-term risk of MACE has been noted among patients who have undergone surgical repair of AAA and/or excluding aneurysm-related events. For example, one retrospective study of 320 patients undergoing endovascular AAA repair found that subsequent to repair an estimated 89.4% of patients will survive free of MACE at 1 year, falling to 59.8% of patients at 5 years.[13] The persistence of increased risk of MACE well beyond AAA repair has led to the suggestion that AAA may represent an independent predictor of cardiovascular mortality. [5,6,12,14,15]

Existing literature regarding AAA and risk of MACE is subject to several shortcomings. The relevant body of literature is comprised in large part of studies which examine outcomes following AAA-related intervention, typically endovascular or open surgical repair.[13,2,16,17] As such, many studies fail to include adequate controls, including people who do not have AAA or

who do not undergo AAA-related intervention. Moreover, population-based studies involving AAA, including (but not limited to) the Framingham Heart Study, have been substantially underpowered with regards to women and non-white, non-European populations.[4,14] The majority of existing longitudinal studies of participants with AAA have a mean follow-up period of 10 years or less, which may not be sufficient to fully describe all meaningful CVD risk endpoints. Finally, increasing use of MACE alone as a clinical endpoint has the potential to obscure which, if any, of the underlying components of this composite measure may contribute disproportionately to outcomes among patients with AAA.

Against this background, an improved understanding of the contemporary risk of MACE among people with AAA is needed. Data from the Atherosclerosis Risk in Communities (ARIC) Study, which includes a large, diverse, community-based cohort, will contribute to filling this gap in the literature.[18] The ARIC study population includes a large cohort of participants identifying as African American, in addition to White participants, with a follow-up period of more than 20 years. Moreover, ascertainment of the majority of AAA cases in ARIC occurred either incidentally during the course of a patient's care, or through clinical manifestation of AAA symptoms, rather than through population screening at an arbitrary time point (although a smaller number of AAA were ascertained via population screening at visit 5). ARIC data will therefore allow for a more pragmatic longitudinal study of MACE risk following AAA ascertainment compared to existing studies, potentially bolstering external validity. Finally, concurrent analysis of individual components of MACE will help to elucidate whether MI, stroke, or all-cause mortality may represent meaningful targets for preventive care. Findings will help inform management of cardiovascular risk factors among patients with AAA, which remains an area of significant inconsistency among major clinical practice guidelines.[19,20,21]

5. Main Hypothesis/Study Aims:

We propose to utilize ARIC data to examine differences in risk of MACE and its components between study participants with and without AAA. We hypothesize that:
1) Having a diagnosis of AAA will be associated with a greater risk of MACE and its components.
2) The association between AAA and MACE will persist after accounting for participants who have undergone surgical repair of AAA.
3) The strongest magnitude of association among MACE components will be found between AAA and overall mortality; however, independent associations will also exist between diagnosis of AAA, MI and stroke.

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

a) inclusion/exclusion

Inclusion:

- All ARIC participants who attended visit 1

Exclusion:

- Race other than white or African American
- Prior AAA surgery at time of visit 1
- History of prior MI or stroke at time of visit 1

- Missing data on covariates of interest

b) Study design

Incident clinical AAA will be modeled as a time-varying event. By event follow-up to 2020 supplemented by CMS data, we have identified a total of 833 clinical AAAs since visit 1 (partly contributed by the ARIC AAA ancillary study AS 2009.18). The outcomes (i.e. MI, stroke, death, as well as the composite MACE outcome) will be analyzed separately. Covariates will be modeled as fixed variables from baseline measurements only. Participants without history of MI/Stroke and AAA diagnosis will contribute person-time into the "non-AAA" category until the first occurrence of either MI, stroke, death, or end of study follow-up, whichever occurred first. If participants are diagnosed with AAA prior to censoring (date of MI, stroke, death from any cause, or end of study follow-up), they will begin contributing person-time to the "AAA" category until the first occurrence of either MI, stroke, death, or end of study follow-up.

c) outcome and other variables of interest with specific reference to the time of their collection

The primary outcomes will be:

- Incident MI
- Incident stroke
- Death from any cause
- A composite MACE indicator (any of the above three)
- Fatal CHD

Of note, CHD and stroke will be based on cases that have been adjudicated by ARIC physicians.

Other variables of interest will be measured at baseline:

- Demographic: age, race, sex, field center, education level
- Smoking status and pack-years of smoking
- BMI
- Comorbid conditions: diagnosis of hypertension, diagnosis of diabetes, use of lipid-lowering medications, use of aspirin
- Surgical repair of AAA, either open (defined as a new ICD-9 procedure code 38.44 or new ICD-10 procedure code 04Q00ZZ) or endovascular (defined as a new ICD-9 procedure code 39.71 or new ICD-10 procedure codes 04Q03ZZ or 04Q04ZZ)
- AAA rupture, defined as a new ICD-9-CM code 441.3 or ICD-10-CM code I71.3

d) summary of data analysis

1. Baseline characteristics will be summarized by "AAA" and "non-AAA" category
2. Number of AAA rupture events as well as number and type of surgical AAA repair procedures will be reported for the "AAA" category to contextualize study findings
3. Multivariable Cox regression will be used to explore the association between incident clinical AAA and subsequent risk of MACE and its components. AAA diagnosis will be modeled as a time-varying event, measured at time of AAA diagnosis. Covariates will be modeled as fixed variables, measured at baseline only. Participants who were not diagnosed with AAA during follow-up will contribute person-time to the non-AAA group throughout. Participants who were diagnosed with AAA during follow-up will contribute person-time to the non-AAA group until the date of AAA diagnosis, and then to the AAA group thereafter

until censoring occurred. Participants whose MACE components occurred before AAA diagnosis will contribute person-time to the non-AAA group only.

Covariates will be analyzed as fixed variables measured at baseline visit 1, as opposed to AAA diagnosis which will be modeled as a time-varying event. This approach will help to reduce selection bias that may occur when covariates from the most recent study visit with regard to the diagnosis date of AAA are analyzed.

Cox regression will be used to measure the association between AAA and MACE, as well as between each of the individual components of MACE, adjusting for: age, gender, race, ARIC field center, education level, BMI, smoking status, pack-years of smoking, total cholesterol and HDL cholesterol, diagnosis of hypertension or diabetes, use of lipid lowering medications, and use of aspirin. Test of proportional hazard assumption will be conducted.

Subgroup analysis will be performed according to comorbid conditions (diabetes, hypertension, and smoking status). Additional subgroup analysis of the "AAA" category will be performed comparing participants who underwent surgical repair of AAA (either open or endovascular) to participants with AAA who did not undergo surgical repair. Further sensitivity analysis will be performed, censoring MACEs occurring during hospitalization for AAA to preclude the influence of perioperative complications.

In a secondary analysis, we will analyze covariates as time varying variables. In this approach, covariates from all visits until the censoring date will be incorporated into the model.

e) Any anticipated methodologic limitations or challenges if present

For the majority of incident AAA cases (those ascertained outside of ARIC visit 5 screening), measurement of maximum aortic diameter is not available. This will preclude stratification of participants by size of AAA. AAA status at visit 1, other than the history of abdominal aortic surgery, is not available in ARIC. However, the prevalence of AAA should be low at baseline given the age of participants at visit 1. This issue has been addressed in the ARIC AAA ancillary study AS 2009.18 (R01HL103695) and numerous ARIC publications on AAA.

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)?

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* AS 2009.18 , R01HL103695, PI Weihong Tang

*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.

References:

1. Robertson L, Atallah E, Stansby G. Pharmacological treatment of vascular risk factors for reducing mortality and cardiovascular events in patients with abdominal aortic aneurysm. Cochrane Vascular Group, editor. Cochrane Database Syst Rev. 2017 Jan 12;2017(1). Available from: http://doi.wiley.com/10.1002/14651858.CD010447.pub3
2. Eldrup N, Budtz-Lilly J, Laustsen J, Bibby BM, Paaske WP. Long-term incidence of myocardial infarct, stroke, and mortality in patients operated on for abdominal aortic aneurysms. J Vasc Surg. 2012 Feb;55(2):311–7.
3. Ko KJ, Yoo JH, Cho HJ, Kim MH, Jun KW, Han KD, et al. The Impact of Abdominal Aortic Aneurysm on Cardiovascular Diseases: A Nationwide Dataset Analysis. Int Heart J. 2021 Nov 29;62(6):1235–40.
4. Sharma C, Singh TP, Thanigaimani S, Nastasi D, Golledge J. A Systematic Review and Meta-Analysis of the Incidence and Risk Factors for Major Adverse Cardiovascular Events in Patients with Unrepaired Abdominal Aortic Aneurysms. Biomedicines. 2023 Apr 14;11(4):1178.
5. Tomee SM, Bulder RMA, Meijer CA, van Berkum I, Hinnen JW, Schoones JW, et al. Excess Mortality for Abdominal Aortic Aneurysms and the Potential of Strict Implementation of Cardiovascular Risk Management: A Multifaceted Study Integrating Meta-Analysis, National Registry, and PHAST and TEDY Trial Data. Eur J Vasc Endovasc Surg Off J Eur Soc Vasc Surg. 2023 Mar;65(3):348–57.
6. Brady AR, Fowkes FGR, Thompson SG, Powell JT. Aortic Aneurysm Diameter and Risk of Cardiovascular Mortality. Arterioscler Thromb Vasc Biol. 2001 Jul;21(7):1203–7.
7. Freiberg MS, Arnold AM, Newman AB, Edwards MS, Kraemer KL, Kuller LH. Abdominal Aortic Aneurysms, Increasing Infrarenal Aortic Diameter, and Risk of Total Mortality and Incident Cardiovascular Disease Events. Circulation. 2008 Feb 26;117(8):1010–7.
8. Duncan JL, Harrild KA, Iversen L, Lee AJ, Godden DJ. Long term outcomes in men screened for abdominal aortic aneurysm: prospective cohort study. The BMJ. 2012 May 4;344:e2958.

9. Forsdahl SH, Solberg S, Singh K, Jacobsen BK. Abdominal aortic aneurysms, or a relatively large diameter of non-aneurysmal aortas, increase total and cardiovascular mortality: the Tromsø study. Int J Epidemiol. 2010 Feb;39(1):225–32.
10. Sharma A, Pagidipati NJ, Califf RM, McGuire DK, Green JB, Demets D, et al. Impact of Regulatory Guidance on Evaluating Cardiovascular Risk of New Glucose-Lowering Therapies to Treat Type 2 Diabetes Mellitus. Circulation. 2020 Mar 10;141(10):843–62.
11. Bosco E, Hsueh L, McConeghy KW, Gravenstein S, Saade E. Major adverse cardiovascular event definitions used in observational analysis of administrative databases: a systematic review. BMC Med Res Methodol. 2021 Dec;21(1):241.
12. Sidloff DA, Saratzis A, Thompson J, Katsogridakis E, Bown MJ. Editor's Choice – Infra-Renal Aortic Diameter and Cardiovascular Risk: Making Better Use of Abdominal Aortic Aneurysm Screening Outcomes. Eur J Vasc Endovasc Surg. 2021 Jul;62(1):38–45.
13. Diender E, Vermeulen JJM, Pisters R, Van Schaik PM, Reijnen MMPJ, Holewijn S. Major adverse cardiac events after elective infrarenal endovascular aortic aneurysm repair. J Vasc Surg. 2022 Dec;76(6):1527-1536.e3.
14. Qazi S, Massaro JM, Chuang ML, D'Agostino RB, Hoffmann U, O'Donnell CJ. Increased Aortic Diameters on Multidetector Computed Tomographic Scan Are Independent Predictors of Incident Adverse Cardiovascular Events: The Framingham Heart Study. Circ Cardiovasc Imaging. 2017 Dec;10(12):e006776.
15. Norman PE, Muller J, Golledge J. The cardiovascular and prognostic significance of the infrarenal aortic diameter. J Vasc Surg. 2011 Dec 1;54(6):1817–20.
16. Hammo S, Grannas D, Wahlgren CM. High Risk of Early and Late Cardiovascular Events After Endovascular Aortic Aneurysm Repair. Ann Vasc Surg. 2022 Oct;86:320–7.
17. Swerdlow NJ, Liang P, Li C, Dansey K, O'Donnell TFX, De Guerre LEVM, et al. Stroke rate after endovascular aortic interventions in the Society for Vascular Surgery Vascular Quality Initiative. J Vasc Surg. 2020 Nov;72(5):1593–601.
18. Tang W, Yao L, Roetker NS, Alonso A, Lutsey PL, Steenson CC, et al. Lifetime Risk and Risk Factors for Abdominal Aortic Aneurysm in a 24 Year Prospective Study: the ARIC Study. 2017;
19. Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, et al. Management of Abdominal Aortic Aneurysms Clinical Practice Guidelines of the European Society for Vascular Surgery. Eur J Vasc Endovasc Surg. 2011 Jan 1;41:S1–58.
20. Wanhainen A, Van Herzeele I, Bastos Goncalves F, Bellmunt Montoya S, Berard X, Boyle JR, et al. Editor's Choice -- European Society for Vascular Surgery (ESVS) 2024 Clinical Practice Guidelines on the Management of Abdominal Aorto-Iliac Artery Aneurysms. Eur J Vasc Endovasc Surg. 2024 Feb;67(2):192–331.
21. Chaikof EL, Dalman RL, Eskandari MK, Jackson BM, Lee WA, Mansour MA, et al. The Society for Vascular Surgery practice guidelines on the care of patients with an abdominal aortic aneurysm. J Vasc Surg. 2018 Jan;67(1):2-77.e2.

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