ARIC Manuscript Proposal #4137

PC Reviewed: 10/11/22 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Carotid artery atherosclerosis for the allocation of aspirin for the primary prevention of cardiovascular disease events: The Multi-Ethnic Study of Atherosclerosis (MESA) and the Atherosclerosis Risk in Communities Study (ARIC)

b. Abbreviated Title (Length 26 characters): Carotid artery atherosclerosis for aspirin allocation

2. Writing Group:

Writing group members:

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

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3. Timeline: Since data is available, manuscript preparation is expected to be complete within 12 months after approval.

4. Rationale:

The role of aspirin in the primary prevention of atherosclerotic cardiovascular disease (ASCVD) events is currently controversial (1,2). Since 2018, three landmark randomized controlled trials and 2 large meta-analyses have suggested a limited benefit of low-dose aspirin for the primary prevention of ASCVD events, which on average is offset by an increased risk of bleeding in elderly individuals, and in those at higher baseline haemorrhagic risk (3-6). Still, in the largest primary prevention meta-analysis available to date, a nonnegligible 11% relative risk reduction (RRR) in ASCVD events was observed for aspirin (7). Given these updated data, the 2019 American College of Cardiology/American Heart Association (ACC/AHA) guidelines for primary prevention were updated to convey recommendations for aspirin use for primary prevention, from a previous class I to a much more tentative IIb recommendation "among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk." (8). It remains unclear, however, how clinicians should best identify patients who are likely to derive a net benefit from aspirin therapy in routine primary prevention. For example, the United States Preventive Services Task Force (USPSTF) provides only a Grade C recommendation to initiate low-dose aspirin for adults aged 40-59 years old with a 10-year ASCVD risk of 10%, stating that the net benefit of aspirin in this group may be small.

In a 2014 analysis in the Multi-Ethnic Study of Atherosclerosis (MESA) (9), Miedema and colleagues used assumptions based on a 2009 aspirin metanalysis, and observed that in asymptomatic individuals with a CAC score ≥100, the estimated 5-year number needed to treat (NNT_5) was 173 for individuals with <10% 10-year estimated risk using the Framingham Risk Score (FRS) and 92 for those ≥10% FRS. For participants with CAC =0, the estimated NNT_5 was 2,036 for individuals <10% FRS, and 808 for individuals ≥10% FRS. While considering all CAC groups, the estimated 5-year number needed to harm (NNH_5) was 442 for a major bleeding (this NNH was an estimate for all study participants, i.e., and was not stratified by either FRS or CAC, and was not based on observed bleeding data from MESA). These estimates suggested that, based on the data as of 2014, CAC could have a valuable role helping identify patients most likely to get net benefit from chronic aspirin therapy.

In a recent 2020 MESA analysis (10), Cainzos-Achirica and colleagues observed that only 5% of MESA participants would qualify for aspirin consideration for primary prevention according to the 2019 AHA/ACC guidelines and using >20% estimated ASCVD risk to define higher risk. Benefit/harm calculations were restricted to aspirin-naive participants <70 years of age not at high risk of bleeding (n=3540). Observed bleeding data was used from MESA further enhance the modelling of bleeding risk. In the overall study population, NNT_5 with aspirin to prevent one cardiovascular disease event was 476 and the NNH_5 was 355. The NNT_5 was also greater than or similar to the NNH_5 among all estimated ASCVD risk strata. Conversely, CAC≥100 and CAC≥400 identified subgroups in which NNT_5 was lower than NNH_5. This was true both overall (for CAC≥100, NNT_5=140 versus NNH_5=518) and within ASCVD risk strata. Also, CAC=0 identified subgroups in which the NNT_5 was much higher than the NNH_5 (overall, NNT_5=1190 versus NNH_5=567).

While the Cainzos-Achirica analyses were influential, with the conclusions incorporated into new guidelines from the National Lipid Association, many clinicians around the world do not

have access to CAC. In many countries, including many from South America and Europe, the utilization of carotid ultrasound is much more prevalent than CAC. For example, the most recent ESC/EAS dyslipidemia guidelines provide a IIa recommendation to use carotid ultrasound for primary prevention ASCVD risk stratification, whereas CAC has a IIb recommendation(11).

Given the interest in using imaging biomarkers to inform my precise use of pharmacotherapy in primary prevention, the aim of the present analysis will be to update the assessment of the role of aspirin in primary prevention as a function of the degree of subclinical carotid atherosclerosis. To enhance statistical power, we will combine data from two landmark NHLBI prospective cohorts – MESA and ARIC.

5. Main Hypothesis/Study Questions:

In a multi-cohort (MESA and ARIC) contemporary, multi-ethnic, community-based US population of asymptomatic adults:

1) What is the number and proportion of men and women of different ages, estimated 10-year ASCVD risk, and baseline carotid atherosclerosis burden who would be eligible for aspirin use for primary ASCVD prevention purposes according to the 2019 ACC/AHA and 2021 USPSTF prevention guidelines?
2) In patients age <70 years and with no known high bleeding risk features, what is the estimated NNT_5 with aspirin to prevent 1 hard CHD event, and the NNT_5 to prevent 1 hard CVD event, respectively and how do these vary by baseline carotid atherosclerosis burden and baseline 10-year estimated ASCVD risk categories (<5%, 5 – 20%, >20%)?
3) In patients age <70 years and with no known high bleeding risk features, what is the estimated NNH_5, when treated with aspirin, to cause 1 bleeding event and how does this vary by baseline carotid atherosclerosis burden and baseline 10-year estimated ASCVD risk categories (<5%, 5 – 20%, >20%)?
4) What is the balance between NNT_5 and NNH_5, both overall as well as by baseline carotid atherosclerosis burden?

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: This is a prospective study that leverages ARIC carotid ultrasound data.

Study population:
MESA and ARIC participants free of clinically-overt ASCVD at the time of recruitment (12). All MESA and ARIC participants with baseline (for MESA Visit #1 and ARIC Visit #1 or #4) information on carotid atherosclerosis burden as elsewhere described in detail(13,14)), aspirin use, and on the variables used by the Pooled Cohort Equations (PCE; age, sex, race/ethnicity, blood pressure, serum cholesterol levels, history of diabetes, tobacco use, medication use for hypertension, statin use) will be considered for inclusion (i.e., individuals with missing information on any of these variables will not be included in the study population). In addition, participants with missing follow-up information will be excluded from the analyses.

Briefly for carotid plaque presence (0 or 1), and carotid atherosclerosis burden, plaque will be defined as a focal abnormal wall thickness (intima-media thickness (IMT), >1.5 mm) or a focal thickening of >50% of the surrounding IMT (15,16). Among participants with adequate imaging data available, a total plaque score (range, 0–12) will be used to describe carotid plaque burden (13). A plaque score has already been defined in MESA. Here, carotid ultrasound data from both ARIC and MESA participants will be harmonized, as both cohorts defined plaque similarly (abnormal wall thickness as above, abnormal shape, or abnormal wall texture) and collected imaging data on from the same anatomic locations: bilateral distal common carotid, carotid bifurcation/bulb, and internal carotid arteries including either the far or the near and far arterial walls (i.e. three to six sites per side per patient [if just 3 scores will be scaled by a factor of 2], therefore harmonized scaled score will range from 0-12). The following ARIC datasets will be used: UBMD4, UBMDBF02, UBMG42, UBMGBF01.

For the incident event, NNT, and NNH analyses, because the focus of the present study is on the allocation of aspirin therapy (guided by carotid atherosclerosis burden) participants already under chronic therapy with aspirin at baseline (defined as any aspirin dose taken 3 or more times per week) will be excluded. Also, these analyses will be restricted to the subgroup of participants <70 years of age and with no high risk bleeding features.

The flow of the study population will be presented as manuscript's **Figure 1**.

Exposures:
For the incident events, Cox regression, NNT, and NNH analyses, patients will be primarily classified based on their baseline carotid atherosclerosis presence/burden. Patients will be further stratified using three 10-year estimated ASCVD risk categories (computed using the PCE): <5%, 5 – 20%, >20%.

Other relevant baseline variables
The following variables assessed at baseline will also be used for the analyses: race/ethnicity, MESA/ARIC site, education level (using 3 categories), cigarette smoking status (current/former/never), pack-years of tobacco use, body mass index (in kg/m^2), low-density and high-density lipoprotein cholesterol levels (both in mg/dL), baseline statin use (yes/no), systolic and diastolic blood pressure (both in mmHg), antihypertensive medication (yes/no), family history of myocardial infarction (yes/no), and type 2 diabetes. diabetes will be defined as any of the following: a history of diabetes, the use of glucose-lowering medications, and/or baseline fasting blood glucose levels ≥126 mg/dL (all at baseline). These will be included as covariates in Cox Proportional Hazards multivariable regression models.

Outcomes
The events of interest will be hard coronary heart disease (CHD) events and hard CVD events. Hard CHD events will be defined as a non-fatal myocardial infarction, death from CHD, or resuscitated cardiac arrest. Hard stroke events will be defined as fatal or non-fatal stroke. Hard CVD events will be defined as hard CHD events plus fatal/non-fatal stroke, other atherosclerotic death, or other CVD death (12). Given recent evidence indicating that all symptomatic focal cerebral ischemic events induce brain damage and should therefore be considered as cerebral

infarctions, we will conduct a sensitivity analysis that includes both hard stroke and transient ischemic attack within the cerebrovascular disease event.

As in prior studies, hospitalized major bleeding events will be defined by hospitalizations using ICD-9 and ICD-10 codes at discharge summary (detailed in table below).

Statistical analysis plan:
In the overall study population:
1) Number and proportion of individuals in whom aspirin could be considered for primary prevention purposes according to the 2019 ACC/AHA primary prevention guideline recommendations (8), i.e., individuals with estimated 10-year ASCVD risk using the PCE >20% + age <70 years + absence of increased bleeding risk features (Figure 2). This will be presented overall as well as by sex, 10 year age strata, baseline estimated 10-year ASCVD risk, and baseline carotid presence/burden.

In the subgroup of participants not treated with aspirin at baseline, who are <70 years of age and who have no high-risk bleeding features (i.e., patients in whom aspirin could be considered):

2) Baseline characteristics of the study participants, overall and by baseline carotid plaque presence/burden. Categorical variables will be presented as number (%), and continuous variables as mean (SD) or median (IQR). Differences between carotid atherosclerosis burden strata will be tested using chi-square tests, ANOVA and nonparametric tests, as needed (Table 1). In supplementary analyses, results will be presented stratified by baseline estimated 10-year ASCVD risk (Table S1), as well as by carotid atherosclerosis burden + 10-year ASCVD risk simultaneously (Table S2).

3) Frequency of estimated 10-year ASCVD risk categories (<5%, 5 – 20%, >20%) overall and by carotid atherosclerosis presence and burden groups (Figure 3A); and frequency of baseline carotid atherosclerosis presence or burden, overall and by estimated 10-year ASCVD risk categories (<5%, 5 – 20%, >20%) (Figure 3B). Results will be presented in %, and differences between strata will be tested using chi-square tests.

4) Unadjusted Kaplan Meier survivor function curves for hard CHD, stroke, and hard CVD events, overall, by baseline carotid atherosclerosis burden, and further categorized by baseline estimated 10-year ASCVD risk (Figures 4, S1 and S2). Log-rank tests will be used to compare the survivor function curves for each of the outcomes across strata. Further categorization by sex and 10-year age strata will be considered and decided upon based on the size of the resulting subgroups (if done, these will be presented in Supplementary tables).

5) Crude incidence rates of hard CHD, stroke and hard CVD events, overall, by baseline carotid atherosclerosis presence/burden, and further categorized by baseline estimated 10-year ASCVD risk (Table 2). Further categorization by sex and age strata will be considered and decided upon based on the size of the resulting subgroups (if done, these will be presented in Supplementary tables).

6) Hazard ratios for hard CHD, stroke and hard CVD events will be calculated for carotid atherosclerosis >0 as compared to carotid atherosclerosis =0 (reference group), overall and by estimated ASCVD risk strata. These analyses will be conducted 1) unadjusted, 2) adjusting for the ASCVD risk factors included in the PCE (including diabetes) plus statin use, and 3) further adjusting for additional ASCVD risk factors not included in the PCE (Table 3).

7) NNT calculations: Assuming an expected 5-year 11% reduction in CVD events with aspirin (7), this will be applied as relative risk reduction to the overall event rates in the study population (i.e., both sexes combined) as well as to strata defined by baseline estimated 10-year ASCVD risk (calculated using the PCE) and carotid atherosclerosis burden. Using the reciprocal of the absolute risk reductions with aspirin, the NNT5 will be calculated (Table 4).

8) NNH calculations: Using the observed rates of bleeding events in MESA and ARIC in each of the subgroups of interest (carotid atherosclerosis/ASCVD risk strata), and assuming an expected 43% 5-year relative risk of major bleeding events (7), the absolute risk increase will be calculated, and the NNH will be computed as the reciprocal. Major bleeding events in MESA and ARIC will be identified using definitions based on International Classification of Diseases (ICD) 9/10 codes (17) for hospitalization for bleeding (Table 5).

9) The NNT5 and NNH5 will be compared graphically in order to characterize the net benefit of aspirin therapy, both overall as well as among carotid atherosclerosis burden (Figure 5).

10) The NNT5 and NNH5 analysis will be repeated also for CHD and stroke events, using meta-analytic 6.6-year relative risk data from Mahmoud et al (6), and Altman-Anderson's method to adjust to 5 years (18) (Supplementary tables).

11) Steps 7 to 9 will be repeated for men and women separately using sex-specific RRR information. In a sensitivity analysis, alternative cut-offs to define "uncontrolled hypertension" will be used.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ 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 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? ___ Yes __X__ 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 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/mantrack/maintain/search/dtSearch.html

___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)?**

There are no relevant existing ARIC manuscript proposals assessing carotid artery atherosclerosis for the allocation of aspirin for the primary prevention of cardiovascular disease events.

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* 2022.11**)**

___ 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 https://sites.cscc.unc.edu/aric/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 http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

References

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ICD-9 (left) and ICD-10 (right) codes used to identify major bleeding events among hospitalized participants

CENTRAL NERVOUS SYSTEM	
Subarachnoid hemorrhage (430) Intracerebral hemorrhage (431) Other and unspecified intracranial hemorrhage (432) Nontraumatic extradural hemorrhage (432.0) Subdural hemorrhage (432.1) Unspecified intracranial hemorrhage (432.9) Subarachnoid, subdural, and extradural hemorrhage, following injury (852) Other and unspecified intracranial hemorrhage following injury (853)	Subarachnoid hemorrhage (I60) Subarachnoid hemorrhage from carotid siphon and bifurcation (I60.0) Subarachnoid hemorrhage from middle cerebral artery (I60.1) Subarachnoid hemorrhage from anterior communicating artery (I60.2) Subarachnoid hemorrhage from posterior communicating artery (I60.3) Subarachnoid hemorrhage from basilar artery (I60.4) Subarachnoid hemorrhage from vertebral artery (I60.5) Subarachnoid hemorrhage from other intracranial arteries (I60.6) Subarachnoid hemorrhage from intracranial artery, unspecified (I60.7) Other subarachnoid hemorrhage (I60.8) Subarachnoid hemorrhage, unspecified (I60.9) Intracerebral hemorrhage (I61) Intracerebral hemorrhage in hemisphere, subcortical (I61.0) Intracerebral hemorrhage in hemisphere, cortical (I61.1) Intracerebral hemorrhage in hemisphere, unspecified (I61.2) Intracerebral hemorrhage in brain stem (I61.3) Intracerebral hemorrhage in cerebellum (I61.4) Intracerebral hemorrhage, intraventricular (I61.5) Intracerebral hemorrhage, multiple localized (I61.6) Other intracerebral hemorrhage (I61.8) Intracerebral hemorrhage, unspecified (I61.9) Other nontraumatic intracranial hemorrhage (I62) Subdural hemorrhage (acute) (nontraumatic) (I62.0) Nontraumatic extradural hemorrhage (I62.1) Intracranial hemorrhage (nontraumatic), unspecified (I62.9) Epidural hemorrhage (S06.4) Traumatic subdural hemorrhage (S06.5) Traumatic subarachnoid hemorrhage (S06.6)
CARDIOVASCULAR	
Other disorders of circulatory system (459) Hemorrhage, unspecified (459.0)	
GASTROINTESTINAL	
Gastro-esophageal laceration-hemorrhage syndrome (530.7) Gastric ulcer (531) Acute with hemorrhage (531.0) Acute with hemorrhage and perforation (531.2) Chronic or unspecified with hemorrhage (531.4) Chronic or unspecified with hemorrhage and perforation (531.6) Duodenal ulcer (532) Acute with hemorrhage (532.0) Acute with hemorrhage and perforation (532.2) Chronic or unspecified with hemorrhage (532.4) Chronic or unspecified with hemorrhage and perforation (532.6) Peptic ulcer, site unspecified (533) Acute with hemorrhage (533.0) Acute with hemorrhage and perforation (533.2) Chronic or unspecified with hemorrhage (533.4) Chronic or unspecified with hemorrhage and perforation (533.6) Gastrojejunal ulcer (534) Acute with hemorrhage (534.0)	Gastroesophageal laceration-hemorrhage syndrome (K22.6) Gastric ulcer (K25) Acute with hemorrhage (K25.0) Acute with both hemorrhage and perforation (K25.2) Chronic or unspecified with hemorrhage (K25.4) Chronic or unspecified with both hemorrhage and perforation (K25.6) Duodenal ulcer (K26) Acute with hemorrhage (K26.0) Acute with both hemorrhage and perforation (K26.2) Chronic or unspecified with hemorrhage (K26.4) Chronic or unspecified with both hemorrhage and perforation (K26.6) Peptic ulcer, site unspecified (K27) Acute with hemorrhage (K27.0) Acute with both hemorrhage and perforation (K27.2) Chronic or unspecified with hemorrhage (K27.4) Chronic or unspecified with both hemorrhage and perforation (K27.6) Gastrojejunal ulcer (K28) Acute with hemorrhage (K28.0)

Acute with hemorrhage and perforation (534.2) Chronic or unspecified with hemorrhage (534.4) Chronic or unspecified with hemorrhage and perforation (534.6) Hemorrhage of rectum and anus (569.3) Hemorrhage of gastrointestinal tract, unspecified (578.9)	Acute with both hemorrhage and perforation (K28.2) Chronic or unspecified with hemorrhage (K28.4) Chronic or unspecified with both hemorrhage and perforation (K28.6) Hemorrhage of anus and rectum (K62.5) Gastrointestinal hemorrhage, unspecified (K92.2)
GENITOURINARY	
Hemorrhage into bladder wall (596.7) Congestion or hemorrhage of prostate (602.1) Ovulation bleeding (626.5) Postmenopausal bleeding (627.1)	Congestion and hemorrhage of prostate (N42.1) Other abnormal uterine and vaginal bleeding (N93) Postcoital and contact bleeding (N93.0) Other specified abnormal uterine and vaginal bleeding (N93.8) Abnormal uterine and vaginal bleeding, unspecified (N93.9)
RESPIRATORY	**PULMONARY**
Pulmonary hemorrhage (770.3) Hemorrhage from throat (784.8)	Hemorrhage from respiratory passages (R04) Hemorrhage from throat (R04.1) Hemorrhage from other sites in respiratory passages (R04.8) Hemorrhage from respiratory passages, unspecified (R04.9) Hemorrhage, not elsewhere classified (R58)
POST-PROCEDURE	
Hemorrhage or hematoma complicating a procedure (998.1) Accidental cut, puncture, perforation, or hemorrhage during medical care (E870) Surgical operation (E870.0) Infusion or transfusion (E870.1) Kidney dialysis or other perfusion (E870.2) Injection or vaccination (E870.3) Endoscopic examination (E870.4) Aspiration of fluid or tissue, puncture, and catheterization (any except heart catheterization) (E870.5) Heart catheterization (E870.6) Administration of enema (E870.7) Other (E870.8) Unspecified (E870.9)	Hemorrhage and hematoma complicating a procedure, not elsewhere classified (T81.0) Unintentional cut, puncture, perforation, or hemorrhage during surgical and medical care (Y60) During surgical operation (Y60.0) During infusion or transfusion (Y60.1) During kidney dialysis or other perfusion (Y60.2) During injection or immunization (Y60.3) During endoscopic examination (Y60.4) During heart catheterization (Y60.5) During aspiration, puncture, and other catheterization (Y60.6) During administration of enema (Y60.7) During other surgical and medical care (Y60.8) During unspecified surgical and medical care (Y60.9)