1. Full Title: Gamma prime (γ’) fibrinogen and subclinical cardiovascular disease: The ARIC Study

b. Abbreviated Title (Length 26 characters): γ’ fibrinogen and carotid IMT

2. Writing Group:
Writing group members: Pam Schreiner, Duke Appiah, Aaron Folsom

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

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3. Timeline: Analyses will be completed during Summer 2015, a first draft to coauthors by August 2015 and a final draft to the P&P Committee during Fall 2015

4. Rationale: Fibrinogen has been associated with cardiovascular disease through coagulation and thrombosis in response to inflammation. The association of fibrinogen as an independent predictor of early atherosclerotic disease such as carotid intima-media wall thickness has also been reported in several studies (Chambless et al., 2002; Dobs et
al., 1999; Grebe et al., 2010; Hunt et al., 2002). Associations of fibrinogen with plaque and shadowing have also been observed in ARIC (Nambi et al. 2010). There have been reports that the association differs by race (Pieters et al., 2014), with whites having stronger associations than blacks.

Recently, an isoform of fibrinogen, γ' fibrinogen, has been proposed as a subtype of fibrinogen that may form clinically relevant clots that are more tightly packed and rigid with thinner fibers and low porosity (Mannila et al., 2007). While γ' fibrinogen normally comprises approximately 7% of the total fibrinogen volume, there is wide variability. Levels are directly correlated with obesity and BMI, female sex, insulin resistance, diabetes, glucose, age and triglycerides, and inversely correlated with physical activity and HDL-c (Lovely et al., 2010; Lovely et al., 2013). Improvements in assays have made measuring this isoform in large cohort studies feasible, allowing assessment of γ' fibrinogen’s role as an independent predictor of subclinical atherosclerosis.

5. Main Hypothesis/Study Questions:

1) Is γ' fibrinogen an independent predictor of the sum of the intima-media wall thickness measures after controlling for total fibrinogen and other cardiovascular risk factors in a cohort of middle-aged black and white men and women attending the ARIC Visit 3 exam?
2) Does this association differ by race and/or sex?
3) Do the associations in questions 1 and 2 differ depending on whether the common carotid, the bifurcation or the internal carotid wall thicknesses are considered?
4) In a subset with total fibrinogen measured at Visit 3, is the γ' fibrinogen/total fibrinogen ratio a superior predictor of the association with carotid IMT?

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).

Analyses will be conducted for those participants who attended the third ARIC visit. Because fibrinogen was only measured in the entire cohort at Visit 1, γ’ fibrinogen will be considered as an independent variable rather than the ratio measure used in several previous studies. Individuals with prevalent CVD will be excluded.

The distribution of γ’ fibrinogen will be examined for normality, and if it is relatively normally distributed, the association between γ’ fibrinogen and the sum of the average carotid IMT measures across left and right common carotid, bifurcation and internal carotid will be considered using γ’ fibrinogen as a continuous variable. If normality is violated, the data will be examined in tertiles of γ’ fibrinogen. Linear regression will be used to assess the mean difference in IMT values either for a 1-sd increment in γ’
fibrinogen or difference between tertiles. These crude analyses will be repeated for region-specific IMT.

The crude models will be adjusted for total fibrinogen. Then the next models will adjust for race, sex, age, smoking, physical activity, field center, lipids and lipid-lowering medications, BMI, diabetes, education, blood pressure and antihypertensive medication use as well as D-dimer, c-reactive protein and factor XI; for women, additional adjustment will include menopause and hormone replacement. Additive interactions for race and for sex will also be examined with a two-tailed p-value of 0.05 being considered as statistically significant.

The above analyses will be repeated for the presence or absence of plaque and shadowing, using logistic regression in place of linear regression, and multiplicative interactions for race and for sex.

Because the proportion of γ’ fibrinogen varies, a secondary analysis will consider the 1011 individuals who also had total fibrinogen measured at Visit 3 to define the ratio of γ’ fibrinogen/total fibrinogen at the same time point. This will be compared to the results of the analyses that used fibrinogen at Visit 1.

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_OTH = “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.)

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 file ICTDER03 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.csc.unc.edu/ARIC/search.php
   __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)?

Yes, Aaron Folsom’s proposal entitled “Associations of γ’ fibrinogen, factor XI and D-dimer with venous thromboembolism and atherothrombotic CVD” and Duke Appiah’s proposal entitled “γ’ fibrinogen and incident cardiovascular outcomes: The ARIC Study”. Both Dr. Folsom and Dr. Appiah are coauthors on this proposal, which excludes clinical CVD and focuses on subclinical disease.

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
___ A. primarily the result of an ancillary study (list number* __________)
___X__ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* ___Data from LITE_______
__________ __________)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

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:


