ARIC Manuscript Proposal #2661

PC Reviewed: 11/10/15	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1a. Full Title: Association of von Willebrand factor deficiency with carotid artery thickness: The Atherosclerosis Risk in Communities Study.

1b. Abbreviated Title (Length 26 characters): VWF deficiency and CVD

2. Writing Group:
Writing group members: Craig Seaman, Margaret Ragni, Kristen George, and Aaron Folsom.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. CS

First author:	Craig Seaman
Address:	3636 Blvd of the Allies
	Pittsburgh, PA 15213
Phone:	412-209-7280
Fax:	412-209-7281
E-mail:	seaman@upmc.edu

3. Timeline: Begin analysis following ARIC committee approval.

4. Rationale:

Von Willebrand factor (VWF), a large multimeric glycoprotein primarily synthesized in vascular endothelial cells, plays a critical role in primary hemostasis. VWF is released from secretory granules and binds to subendothelial collagen at the site of vascular injury. There it facilitates platelet adhesion by binding to the glycoprotein Ib-IX-V receptor complex. VWF binding leads to platelet activation and aggregation. This process is most effective at high shear rates, where a conformational change in VWF multimers enhances platelet binding. In addition to its well-defined role in thrombus formation during the rupture of atherosclerotic plaques, VWF may play a role in the pathogenesis of atherosclerosis by direct participation in plaque formation. These findings suggest VWF may modify the risk of cardiovascular disease (CVD).

Several prospective cohort studies have examined the role of VWF in CVD. Despite differences in study design, population, and definition of CVD (coronary heart disease, myocardial infarction, ischemic stroke, intermittent claudication, etc.), most studies concluded a positive, albeit weak, association between plasma VWF levels and CVD after adjusting for several well-established CVD related risk factors. However, it remains uncertain if a true cause and effect relationship exists, or if increased plasma VWF levels represent a marker of endothelial damage and inflammation in patients with underlying atherosclerotic disease.

Given the potential role of increased plasma VWF levels in CVD, it is logical to reason VWF deficiency may protect against CVD. Von Willebrand disease (VWD) is an inherited bleeding disordered characterized by VWF deficiency or dysfunction. Several studies have shown reduced aortic and carotid atherosclerosis in VWF deficient pigs. A few small observational studies examining the association between VWD and atherosclerosis in humans found no clear protection afforded by VWD; however, a myriad of factors, including heterogeneous patient population and small cohort size, may have precluded interpretation of study results. More recently, a cross-sectional study in the Netherlands performed by Sanders *et al* reported a reduced prevalence of arterial thrombosis in VWD compared with the general population providing evidence that VWF deficiency may protect against CVD. Similarly, an analysis of a national discharge register by Seaman *et al* found a 15% decrease in the odds of CVD in VWD patients.

While a great deal of research has been done to show elevated plasma VWF levels are associated with a slight increased risk of CVD, little research has been done to determine if VWF deficiency is protective against CVD. Moreover, the majority of studies performed to date have been limited by small sample size and other factors. If VWF deficiency is truly protective against CVD, it will lend support that VWF may function as a therapeutic target in the prevention and treatment of CVD. Further, it will provide evidence that VWF deficiency is a mitigating factor in CVD and open the possibility for less intensive therapy with antiplatelet agents, and other similar medications, which may only serve to further increase the risk of bleeding in this population of patients.

5. Main Hypothesis/Study Questions:
We hypothesize that the prevalence of CVD is decreased in patients with VWF deficiency. We aim to compare mean carotid artery intima-media thickness (IMT) among patients with and without VWF deficiency.

6. Design and analysis:
Design: cross-sectional analysis at ARIC baseline. Individuals with missing plasma VWF antigen (VWF: Ag) levels will be excluded.

Exposure: VWF deficiency will be defined as plasma VWF: Ag levels less than 0.50 IU/dL (50%).

Outcome: Mean carotid artery IMT. We will also consider CVD (defined as coronary heart disease, stroke, or claudication) as a secondary outcome.

Other variables: Age, sex, race, hypertension, hyperlipidemia, diabetes mellitus, tobacco use, obesity, fibrinogen, and FVIII.

Among those without prevalent clinical CVD, we will compare the mean carotid artery IMT between participants with and without VWF deficiency using ANCOVA. We also will compare the prevalence of high IMT (above the 90^{th} sex-specific percentiles), using logistic regression. The prevalence of CVD, the secondary analysis, will be compared between those with and without VWF deficiency using logistic regression. Regression analyses will control for the

potential confounding effect of established CVD risk factors on mean carotid IMT and CVD. CVD risk factors will consist of age, sex, race, hypertension, hyperlipidemia, diabetes mellitus, tobacco use, and obesity. If the analysis reveals associations with VWF deficiency, we will explore further whether FVIII level or fibrinogen level may explain the associations.

7. Will the data be used for non-CVD analysis in this manuscript?
No

8. Will the DNA data be used in this manuscript?
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/search.php.
Yes

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)?

Folsom AR, Rosamond WD, Shahar E, et al. Prospective study of markers of hemostatic function with risk of ischemic stroke. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Circulation.* 1999;100(7):736-742.

Folsom AR, Wu KK, Rosamond WD, et al. Prospective study of hemostatic factors and incidence of coronary heart disease: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation.* 1997;96(4):1102-1108.

Folsom AR, Wu KK, Shahar E, et al. Association of hemostatic variables with prevalent cardiovascular disease and asymptomatic carotid artery atherosclerosis. The Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Arterioscler Thromb.* 1993;13(12):1829-1836.

Kucharska-Newton AM, Couper DJ, Pankow JS, et al. Hemostasis, Inflammation, and Fatal and Nonfatal Coronary Heart Disease: Long-Term Follow-Up of the Atherosclerosis Risk in Communities (ARIC) Cohort. *Arterioscler Thromb.* 2009;29:2182-2190.

11. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?
No

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.

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.
No