ARIC Manuscript Proposal #2040

PC Reviewed: 12/11/12	**Status: A**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Carotid Bifurcation Geometry is an Independent Risk Factor for Early Carotid Wall Thickening

b. Abbreviated Title (Length 26 characters): Geometric Risk of Atherosclerosis

2. Writing Group:
Writing group members: Payam Bijari, Bruce Wasserman, David Steinman

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

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3. Timeline:
November 2012 – First draft prepared as part of PhD thesis chapter
December 2012 – complete segmentation of all included cases
January 2013 – Manuscript ready for ARIC review

4. Rationale:

There is little doubt that hemodynamic forces are associated with the development of focal atherosclerotic plaques; however, these forces are difficult to measure directly. Instead, it was proposed by Friedman [Atherosclerosis 1983 Feb;46(2):225-31] that the geometry of the carotid bifurcation, as the primary determinant of local hemodynamics, could be a clinically feasible surrogate "local" risk factor for atherosclerosis. To date this hypothesis has not been satisfactorily tested, owing to small sample sizes (effect of systemic factors) and confounding effect of age/disease on geometry.

Recent evidence from the CARDIA study (N~3000) demonstrates that IMT at the carotid bulb is more weakly associated with conventional CV risk factors than IMT at the common carotid artery [Polak et al. Stroke 2010 Jan;41(1):9-15], which the authors speculated is due to the local geometric/hemodynamic influence at the bulb. As explained below, the ARIC Carotid MRI study provides all of the necessary ingredients to directly confirm this, for the first time.

5. Main Hypothesis/Study Questions:

We hypothesize the certain factors characterizing the shape of the carotid bifurcation are significant predictors of early carotid bulb wall thickening, independent of systemic risk factors. A secondary hypothesis is such significant relationship can only be found by controlling for both systemic risk factors *and* the secondary effect of age/disease on geometry.

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).

Our starting point is the ARIC Carotid MRI wall remodeling study [Astor et al., Radiology 2010 Sep;256(3):879-86], which identified 1064 cases for which CCA and ICA wall thickness from black blood magnetic resonance imaging (BBMRI) and systemic risk factor data are already available in spreadsheet form courtesy of Brad Astor. The only extra ingredient is digital 3D segmentation of the carotid bifurcation lumen from contrast-enhanced magnetic resonance angiograms (CEMRA) acquired at the same time as the black blood MRI scans. Carotid bifurcation segmentation and geometric analysis is done using the automated techniques we have previously published [Bijari et al., J Magn Reson Imaging 2011 Feb;33(2):482-9 and Bijari et al., J Biomech 2012 Jun 1;45(9):1632-7].

Our analysis focuses on two groups, identified from Astor's spreadsheet: those participants with complete systemic risk factor data (based on the same systemic risk factors considered by Polak et al.), sufficient quality CEMRA for digital segmentation, and 0% stenosis severity; and the subset of these with ICA and CCA wall thickness below the threshold for luminal narrowing (based on thresholds from Astor et al.).

Following the approach of Polak et al., multiple linear regression is carried out for each of the two groups with CCA and ICA wall thickness, separately, as dependent variables; and systemic risk factors + local (geometric) factors as independent variables. The expected outcome is that R^2_{adj} will be higher for regressions that include local

geometric factors, and that one or more of these factors will be a significant independent predictor (i.e., β-value with $p<0.05$).

Preliminary results suggest that even with our strict inclusion criteria we may include cases having "abnormal" carotid bifurcation geometries, which may weaken or mask associations with geometric factors we have identified as surrogate markers of disturbed flow in the normal carotid bifurcation. To test this, we considered a subset of cases having "normal" carotid bifurcation geometries according to the descriptive statistics of young adult carotid bifurcation geometry published by Thomas et al. [Stroke. 2005 Nov;36(11):2450-6.]. Preliminary results (table below) demonstrates a strong association with FlareA, a geometric factor that we had previously shown to be a strong predictor of disturbed flow at the carotid bulb. They also confirm Polak et al.'s finding that such local factors would influence ICA wall thickness (WT), but not CCA WT.

	Maximum ICA WT		Mean CCA WT	
New Geometric Factors	β (p-value)	Partial R^2	β (p-value)	Partial R^2
FlareA	0.302 (**0.0001**)	0.104	0.112 (NS)	0.013
Tort2D	-0.231 (**0.020**)	0.045	0.032 (NS)	0.001
Ica Angle	-0.222 (**0.029**)	0.044	-0.064 (NS)	0.003
Bifurcation Angle	0.198 (NS)	0.031	-0.085 (NS)	0.005
Systemic + New Geometric	**R^2 = 0.311 R^2_{adj} = 0.212**		**R^2 = 0.194 R^2_{adj} = 0.078**	
Old Geometric Factors	β (p-value)	Partial R^2	β (p-value)	Partial R^2
AR1	0.167 (NS)	0.030	0.048 (NS)	0.002
Tortuosity	0.136 (NS)	0.013	0.098 (NS)	0.006
Ica Angle	-0.555 (NS)	0.002	-0.032 (NS)	0.001
Bifurcation Angle	0.025 (NS)	0.000	-0.131 (NS)	0.001
Systemic + Old Geometric	**R^2 = 0.246 R^2_{adj} = 0.137**		**R^2 = 0.187 R^2_{adj} = 0.070**	
Systemic Factors Alone	**R^2 = 0.197 R^2_{adj} = 0.112**		**R^2 = 0.171 R^2_{adj} = 0.083**	

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.cscc.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)?

Astor BC, Sharrett AR, Coresh J, Chambless LE, Wasserman BA. Remodeling of carotid arteries detected with MR imaging: atherosclerosis risk in communities carotid MRI study. Radiology. 2010 Sep;256(3):879-86.

Bijari PB, Antiga L, Wasserman BA, Steinman DA. Scan-Rescan reproducibility of carotid bifurcation geometry from routine contrast-enhanced MR angiography. J Magn Reson Imaging. 2011 Feb;33(2):482-9.

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* 2006.14**)**

___ 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 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.