1.a. **Full Title**: Sensitivity of Carotid Artery Plaque Ulcer Detection using Contrast-enhanced and Time-of-Flight MRA Techniques

b. **Abbreviated Title (Length 26 characters)**: MRI for Ulcer Detection

2. **Writing Group**:
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3. **Timeline**: 6-10 Months
4. **Rationale:**

The risk of stroke in patients with carotid atheromatous plaque is not only affected by the size of the plaque and the degree of obstruction but also by the presence of ulceration [1]. Thrombus can form within an ulcer crater due to disturbances of normal flow patterns and this can embolize to the brain leading to an ischemic event [1, 2]. Yukio et al. showed that average peak velocity (APV) and shear index measurements are markedly decreased at the center of a coronary artery aneurysm compared to these measurements acquired in the vessel proximal and distal to the aneurysm neck [3]. The reduction in APV and shear index correlated with increasing aneurysm size, which presumably leads to flow stagnation and initiation of thrombus formation. This relationship between size and risk of thrombus might be applicable to carotid artery ulcers, which are often within the same range of sizes as coronary aneurysms.

Catheter-based angiography historically has been considered the gold standard for carotid artery assessment, which includes measuring stenosis and detecting ulceration. Noninvasive imaging modalities such as MR angiography (MRA) and ultrasound have emerged as adequate alternatives for the assessment of stenosis, with comparable accuracies [4-7]. DSA provides a poor relative standard for these noninvasive techniques when considering the detection of ulceration because of its own limited sensitivity. For example, multicenter studies have shown that there is little agreement between conventional angiographic findings and corresponding surgical specimen observations in the detection of carotid plaque ulceration, with sensitivity and specificity for ulcer detection of 45.9% and 74.1%, respectively [8]. Doppler ultrasound sensitivity to detect carotid plaque ulceration is roughly equivalent to that reported for digital subtraction angiography (DSA). Furthermore, the degree of stenosis caused by the plaque significantly affects the diagnostic sensitivities of these two modalities. The sensitivity of B-mode ultrasound was found to be 77% (10/13) in plaques less than or equal to 50% and 41% (26/63) for plaques greater than 50% (p = 0.03). DSA likewise detected 77% (10/13) of ulcers in plaques less than or equal to 50% stenosis and 48% (30/63) in plaques with greater than 50% stenosis (p = 0.07) [9]. The limited ability of DSA to detect plaque ulceration may be due to the limited views obtained [4]. MRA, on the other hand, allows for multiple projections of the vessel which may improve the sensitivity for ulcer detection [4]. The large number of views in MRA has been the attributable reason for the greater accuracy of stenosis measurements compared with DSA [10].

Although there are several techniques used for MRA, Time-of-Flight (TOF) and contrast-enhanced (CE) techniques are the most widely employed for clinical applications. TOF MRA provides more accurate measurements of carotid artery stenosis; however, CEMRA is more sensitive for detecting narrowing and provides greater coverage of the carotid artery enabling the detection of tandem lesions [11]. Despite these merits of CEMRA, its use is sometimes prohibitive because it requires an intravenous injection of gadolinium. The best approach for detecting ulceration by MRA has not been established and is the primary aim of this study. We expect CE-MRA to be more sensitive since, unlike TOF MRA, it is not prone to signal loss from the saturation of protons recirculating within the crater; however, recirculation may depend on ulcer size. Furthermore, TOFMRA is acquired at higher resolution because of its smaller field of view, and this may enhance its ability to detect small ulcers. The sensitivity for ulcer detection will be compared between TOF and CE MRA techniques and related to the size
of the ulcer crater, which is an important determinant of its likelihood to thrombose and cause a clinical event. The distribution of carotid plaque ulcerations will be determined and generalized to a normal population based on its geometry and degree of stenosis. We will also determine the association of ulceration and clinical evidence of ipsilateral cerebrovascular ischemia based on ulcer size categories controlling for degree of stenosis.

5. **Main Hypothesis/Study Questions:**

1. CE-MRA is more sensitive than TOF MRA for detection of carotid plaque ulceration.
   a. Detection of ulceration on maximum intensity projections (MIPs) will be compared using CEMRA and TOF MRA techniques.
   b. The benefit of reviewing source images in addition to the MIPs will be determined for each technique.
2. We will explore the influence of ulcer size and location on its detection using these MRA techniques.
3. The prevalence of ulcerations based on size categories will be determined and associations between ulcer presence and risk factors and plaque features (e.g., lipid core) will be determined. The relationship between stenosis and the size of the ulcer as well as its location relative to the flow divider will be explored.

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).**

   This is a cross sectional study of ARIC participants with carotid atherosclerosis detected by MRI in Visit 5. A minimum cutpoint for GDSICAMAXWALLTHICK below which no lipid cores were observed will be used for inclusion into this study. Only cases with IQ scores of 1 or 2 (good or adequate) for the CEMRA and TOFMRA sequences will be included. Assuming that results for ulcer presence using CEMRA and TOFMRA are discordant in 25% of studies, a total of 400 studies will provide 80% power to detect a difference in the degree of agreement (with the source image) as small as 40% (e.g., 70% for CEMRA vs. 30% for TOFMRA). For example, this corresponds to agreement with the source images of 92.5% for CEMRA and 82.5% for TOFMRA. An ulcer will be defined as an indentation, fissure or erosion on the luminal surface of a plaque, exposing a portion of the inner plaque to direct contact with circulating blood [12]. We set a lower limit of 2 mm for the width of the ulcer neck.

<table>
<thead>
<tr>
<th>Variable name</th>
<th>Description</th>
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<tbody>
<tr>
<td>CEMIP_UP1</td>
<td>Ulcer Presence detected on CEMRA MIP (1=present, 0=absent)</td>
</tr>
<tr>
<td>TOFMIP_UP2</td>
<td>Ulcer Presence detected on TOF MRA MIP (1=present, 0=absent)</td>
</tr>
<tr>
<td>CESc_UP3</td>
<td>Ulcer Presence confirmed on source images of the CEMRA (1=confirmed, 0=refuted)</td>
</tr>
</tbody>
</table>
TOFSc_UP  Ulcer Presence confirmed on source images of the TOFMRA (1=confirmed, 0=refuted)
UNo_TOF  Number of ulcers detected on the TOFMRA MIPs and source images
UNo_CE  Number of ulcers detected on the CEMRA MIPs and source images
CL  Concordance of ulcer Locations between TOF and CE techniques. This is determined after second reading. 1=concordant; 0=not concordant
STEN_CE  Percent stenosis based on the CEMRA MIPs
STEN_TOF  Percent stenosis based on the TOFMRA MIPs
IQ_CEMRA  Image quality score for the CEMRA (1=adequate, 2=good)
IQ_TOFMRA  Image quality score for the TOFMRA (1=adequate, 2=good)

If UNo_TOF or UNo_CE is equal to 1:
U1_LLongMIP_CE6 Maximum length of the ulcer along the long axis of the vessel (cranio-caudad) on the CEMRA MIP
U1_NLongMIP_CE7 Ulcer neck length along the long axis of the vessel (cranio-caudad) on the CEMRA MIP
U1_D_CEMIP8 Ulcer depth on the CEMRA MIP
U1_LLongMIP_TOF Maximum length of the ulcer along the long axis of the vessel (cranio-caudad) on the TOFMRA MIP
U1_NLongMIP_TOF Ulcer neck length along the long axis of the vessel (cranio-caudad) on the TOF MRA MIP
U1_D_TOFMIP Ulcer depth on the TOFMRA MIP
U1_W_CESc9 Ulcer width on the CEMRA source images
U1_W_TOFSc Ulcer width on the TOFMRA source images
Dist_FDU1_CEMIP10 Distance from the flow divider to the nearest margin of the neck of the ulcer based on the CEMRA MIP (negative value if ulcer is below FD)
Dist_FDU1_TOFMIP Distance from the flow divider to the nearest margin of the neck of the ulcer based on the TOFMRA MIP (negative value if ulcer is below FD)

If UNo_TOF or UNo_CE is greater than 1:
UL_LLongMIP_CE11 Maximum length of the largest ulcer along the long axis of the vessel (cranio-caudad) on the CEMRA MIP
UL_NLongMIP_CE Ulcer neck length (largest ulcer) along the long axis of the vessel (cranio-caudad) on the CEMRA MIP
UL_D_CEMIP6 Ulcer depth (largest ulcer) on the CEMRA MIP
UL_LLongMIP_TOF Maximum length of the largest ulcer along the long axis of the vessel (cranio-caudad) on the TOFMRA MIP
UL_NLongMIP_TOF Ulcer neck length (largest ulcer) along the long axis of the vessel (cranio-caudad) on the TOF MRA MIP
UL_D_TOFMIP Ulcer depth (largest ulcer) on the TOFMRA MIP
UL_W_CESc Ulcer width (largest ulcer) on the CEMRA source images
UL_W_TOFSc  Ulcer width (largest ulcer) on the TOFMRA source images
Dist_FDUL_CEMIP  Distance from the flow divider to the nearest margin of the neck of the largest ulcer based on the CEMRA MIP (negative value if ulcer is below FD)
Dist_FDUL_TOFMIP  Distance from the flow divider to the nearest margin of the neck of the largest ulcer based on the TOFMRA MIP (negative value if ulcer is below FD)
US_LLongMIP_CE$_{12}$  Maximum length of the smallest ulcer along the long axis of the vessel (cranio-caudad) on the CEMRA MIP
US_NLongMIP_CE  Ulcer neck length (smallest ulcer) along the long axis of the vessel (cranio-caudad) on the CEMRA MIP
US_D_CEMIP  Ulcer depth (smallest ulcer) on the CEMRA MIP
US_LLongMIP_TOF  Maximum length of the smallest ulcer along the long axis of the vessel (cranio-caudad) on the TOF MRA MIP
US_NLongMIP_TOF  Ulcer neck length (smallest ulcer) along the long axis of the vessel (cranio-caudad) on the TOF MRA MIP
US_D_TOFMIP  Ulcer depth (smallest ulcer) on the TOFMRA MIP
US_W_CESc  Ulcer width (smallest ulcer) on the CEMRA source images
US_W_TOFSc  Ulcer width (smallest ulcer) on the TOFMRA source images
Dist_FDUS_CEMIP  Distance from the flow divider to the nearest margin of the neck of the smallest ulcer based on the CEMRA MIP (negative value if ulcer is below FD)
Dist_FDUS_TOFMIP  Distance from the flow divider to the nearest margin of the neck of the smallest ulcer based on the TOFMRA MIP (negative value if ulcer is below FD)

$^{1}$CE = Contrast-enhanced MRA; MIP = Maximum Intensity Projection; UP = Ulcer presence
$^{2}$TOF = Time-of-flight MRA
$^{3}$Sc = Source images
$^{4}$No = Number
$^{5}$CL = Concordant location
$^{6}$U1L = Ulcer Length; 1 = single ulcer; Long = Long axis (cranio-caudal) dimension
$^{7}$U1N = Ulcer Neck
$^{8}$U1D = Ulcer Depth
$^{7}$U1W = Ulcer Width
$^{9}$Dist = Distance; FD = Flow Divider
$^{11}$UL = Largest ulcer
$^{12}$US = Smallest ulcer

Note: All measurements (e.g., ulcer dimensions, distance from FD) are in mm.

Method: The ARIC participants from visit 5 have undergone two MR angiographic studies as part of the carotid MRI exam, a contrast-enhanced MRA (CEMRA) and a TOF MRA. Maximum Intensity Projection (MIP) images have already been generate at the Field Sites and sent to the MRI Reading Center along with the remainder of the MRI
study. The CEMRA MIPs and the TOF MIPs of both carotids will be assigned different identification numbers to ensure anonymity of the case. Two readers who are blinded to the objectives of this study and to the clinical information of the participants will interpret the CE-MRA and the TOF-MIPs on separate sessions separated by at least a 2 week interval. Each reader will determine if an ulcer is present and, if identified, record its dimensions and location relative to the flow divider. The source images will then be reviewed and ulcer detection will be confirmed or refuted. If more than one ulcer is seen, the dimensions of the largest and smallest ulcers will be recorded. Following the second session, after both the TOFMRA and CEMRA studies have been evaluated, the reader will check for the correspondence of ulcer locations for the two techniques. Disagreement between readers for ulcer presence based on the MIPs and source data will be arbitrated by Dr. Wasserman.

References:
6. Paul J. Nederkoorn, M.W.P.T.M.M., MD, PhD; Bert C. Eikelboom, MD, PhD; Otto E.H. Elgersma, MD, PhD; Erik Buskens, MD, PhD; M.G. Myriam Hunink, MD, PhD; L. Jaap Kappelle, MD, PhD; Pieter C. Buijs, MD; Aloys F.J. Wüst, MD, PhD; Aad van der Lugt, MD, PhD; Yolanda van der Graaf, MD, PhD, *Preoperative Diagnosis of Carotid Artery Stenosis Accuracy of Noninvasive Testing*. Stroke, 2002. 33: p. 2003-2008.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  ____ No  
   b. If Yes, is the author aware that the file ICTDER02 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 ICTDER02 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  ____ No  
8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 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  
   ____ Yes  ____ No  (There is no overlap)

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 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* _1997.02_)  
   ___ 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/

12. 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.