

# Increased Prevalence of Carotid Artery Atherosclerosis in Rheumatoid Arthritis Is Artery-specific

HITOMI KOBAYASHI, JON T. GILES, JOSEPH F. POLAK, ROGER S. BLUMENTHAL, MARY S. LEFFELL, MOYSES SZKLO, MICHELLE PETRI, ALLAN C. GELBER, WENDY POST, and JOAN M. BATHON

**ABSTRACT Objective.** Cardiovascular (CV) morbidity and mortality are increased in rheumatoid arthritis (RA). Prior investigations of the association of RA with measures of carotid atherosclerosis have yielded conflicting results. We compared carotid intima-media thickness (IMT) of both the common carotid (CCA) and proximal internal carotid (bulb-ICA) arteries, and plaque prevalence, between RA and non-RA participants.

**Methods.** Subjects with RA were participants in a cohort study of subclinical CV disease in RA. Non-RA controls were selected from the Multi-Ethnic Study of Atherosclerosis. Both groups underwent B-mode ultrasonography of the right and left CCA and bulb-ICA. Linear regression was used to model the association of RA status with CCA and bulb-ICA-IMT, and logistic regression for the association of RA status with plaque.

**Results.** We compared 195 RA patients to 198 non-RA controls. CV risk factors were similarly distributed, except for a higher prevalence of hypertension in the RA group. Mean adjusted bulb-ICA-IMT was higher in RA patients than controls (1.16 vs 1.02 mm, respectively;  $p < 0.001$ ), while mean adjusted CCA-IMT did not differ significantly. After adjusting for CV risk factors, the odds of plaque were significantly increased in RA participants compared to controls (OR 2.41, 95% CI 1.26–4.61). The association of gender, age, smoking, and hypertension with bulb-ICA-IMT and plaque did not significantly differ by RA status. Interleukin 6 was strongly associated with bulb-ICA-IMT and plaque in controls but not in RA patients. In the RA group, shared epitope was associated with an increased prevalence of plaque.

**Conclusion.** Compared to controls, RA was associated with a higher prevalence and higher severity of atherosclerosis in the bulb-ICA but not the CCA. Our data suggest that future studies in RA that utilize carotid artery measurements should include assessment of the bulb-ICA. (First Release Feb 1 2010; J Rheumatol 2010;37:730–9; doi:10.3899/jrheum.090670)

## Key Indexing Terms:

RHEUMATOID ARTHRITIS  
CAROTID DISEASE

INFLAMMATION

ATHEROSCLEROSIS  
EPIDEMIOLOGY

Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects 1%–2% of adult populations. RA is associated with a reduced life expectancy compared to the general population<sup>1–4</sup>, primarily due to increased cardiovascular (CV)

morbidity and mortality. Rates of myocardial infarction are 2–3 times higher in RA patients than non-RA controls<sup>1,5,6</sup>, and RA patients are more likely to experience silent ischemia<sup>6</sup>. Adjustment for conventional CV risk factors does not account for the higher rates of CV events in RA populations<sup>1,5,6</sup>, suggesting that rheumatoid inflammation is an independent risk factor for CV disease.

The detection of asymptomatic atherosclerosis in RA may enable identification of individuals at high risk for acute CV events who constitute optimal targets for early intervention. Carotid B-mode ultrasonography is a convenient noninvasive method for detecting subclinical atherosclerosis. Increased intima-media thickness (IMT) and the presence of plaque in the carotid arteries are strongly correlated with CV risk factors and generalized atherosclerosis<sup>7,8</sup>, and are also strong predictors of future stroke and myocardial infarction in the general population<sup>9–11</sup>.

A number of investigations of subclinical carotid artery disease using carotid ultrasonography have been reported in RA, but with conflicting results<sup>12–22</sup>. Most of the non-US

*From the Divisions of Rheumatology, Cardiology, and Immunogenetics, Department of Medicine, and Bloomberg School of Public Health, Johns Hopkins Medical Institutions, Baltimore, Maryland; and Tufts-New England Medical Center, Boston, Massachusetts, USA.*

*Supported by Grant AR 050026-01 (JMB) from the National Institutes of Health, National Institute of Arthritis and Musculoskeletal and Skin Diseases, and contracts N01-HC-95159 through N01-HC-95166 and N01-HC-95169 from the National Heart, Lung, and Blood Institute.*

*H. Kobayashi, MD; J.T. Giles, MD, MPH, Division of Rheumatology, Johns Hopkins Medical Institutions; J.F. Polak, MD, Tufts-New England Medical Center; R.S. Blumenthal, MD, Division of Cardiology; M.S. Leffell, MD, Division of Immunogenetics; M. Szklo, MD, MPH, Bloomberg School of Public Health; M. Petri, MD; A.C. Gelber, MD, PhD, Division of Rheumatology; W. Post, MD, Division of Cardiology; J.M. Bathon, Division of Rheumatology, Johns Hopkins Medical Institutions.*

*Address correspondence to Dr. J.M. Bathon, Division of Rheumatology, Johns Hopkins University School of Medicine, 5200 Eastern Ave., Suite 4100, Baltimore, MD 21224. E-mail: jrbathon@jhmi.edu*

*Accepted for publication October 1, 2009.*

studies have reported significantly higher mean IMT values in RA subjects compared to controls; however, many of these studies were small and thus were unable to adjust adequately for conventional CV risk factors<sup>12-19</sup>. In contrast, 2 large US studies found no difference in mean IMT level between RA and non-RA subjects<sup>20,21</sup>. Similarly, 6 of 8 non-US studies<sup>15,19</sup>, and one of the 2 US studies<sup>20</sup>, found no difference in plaque prevalence between the RA versus non-RA groups. Thus, an unambiguous association of RA with more severe subclinical carotid atherosclerosis has not been clearly demonstrated.

The inconsistency in these study results likely derives from methodological rather than biological differences, the most important of which may be differences in the definitions of plaque and IMT and different locations imaged in the carotid arteries. The internal carotid artery (ICA) and carotid bifurcation are anatomic sites with a predilection for development of atherosclerotic plaque, and some have argued that IMT measures from these sites may be a better estimate of true atherosclerosis than measures obtained from the common carotid artery (CCA)<sup>23</sup>. Despite this, very little is known in RA populations about artery-specific differences in IMT and their relationships to CV risk factors.

The primary aim of our study was to evaluate IMT in different carotid arteries, as well as overall prevalence of carotid plaque, in a large RA cohort and to compare these measures to a contemporaneous non-RA control group using identical protocols. Our secondary aims were: (1) to determine and compare the relationship of these carotid ultrasound variables to traditional and inflammatory CV risk factors in the 2 groups; and (2) to identify disease characteristics associated with higher IMT and greater plaque prevalence within the RA cohort.

## MATERIALS AND METHODS

**Participants and enrollment.** RA subjects. ESCAPE RA (Evaluation of Subclinical Cardiovascular disease And Predictors of Events in Rheumatoid Arthritis) is a cohort study of the prevalence, progression, and risk factors for subclinical CV disease in men and women with RA<sup>24</sup>. It was designed with identical inclusion and exclusion criteria (except for the diagnosis of RA) to those of the Multi-Ethnic Study of Atherosclerosis (MESA), a population-based cohort study of subclinical CV disease with similar objectives. ESCAPE RA inclusion criteria were: (1) fulfillment of American College of Rheumatology criteria for the classification of RA<sup>25</sup> of > 6 months; and (2) age 45–84 years. Exclusion criteria were: (1) prior self-reported physician-diagnosed myocardial infarction, heart failure, coronary artery revascularization, peripheral vascular (arterial) disease or procedures, implanted pacemaker or defibrillator devices, and current atrial fibrillation; (2) weight exceeding 300 pounds (due to imaging equipment limitations); and (3) computerized tomographic scan of the chest within 6 months prior to enrollment (to limit radiation exposure). One hundred ninety-five RA participants were recruited from the Johns Hopkins Arthritis Clinic and by referral from local rheumatologists from October 2004 through May 2006. Informed consent was obtained from all participants, and the study was approved by the Institutional Review Board of the Johns Hopkins Hospital.

**Control subjects.** The controls without RA were selected from MESA participants enrolled in the Baltimore Field Center. Frequency matching was

used to select a control group with similar demographic characteristics as the RA group, using 16 substrata defined by gender (male/female), age (9-year increments), and race (Black/White). A description of MESA design and methods has been published<sup>26</sup>. In brief, MESA enrolled a multi-ethnic cohort of 6814 participants aged 45–84 years without clinically apparent CV disease from 6 US communities between 2000 and 2002, among whom 1086 were enrolled by the Johns Hopkins (Baltimore) Field Center. MESA participants who reported use of disease-modifying antirheumatic drugs (DMARD) that are typically used for the treatment of RA were excluded as potential controls. A total of one hundred ninety-eight MESA controls were available for the analyses.

**Assessments. Carotid imaging.** Ultrasound imaging of the carotid arteries was performed in ESCAPE-RA participants using MESA ultrasound procedures, technicians, and equipment (Logiq 700, General Electric Medical Systems). The probe frequency utilized for the ICA/bulb was 9 MHz, for the CCA 13 MHz, and for the pulsed Doppler studies 4.0 MHz. The imaging protocol involved obtaining a single longitudinal lateral view of the distal 10 mm of the right and left CCA and 3 longitudinal views in different imaging planes of each bulb-ICA. The bulb-ICA was defined as including both the carotid bulb, identified by the loss of parallel wall present in the CCA, and the 10-mm segment of the ICA distal to the tip of the flow divider that separates the external and internal carotid arteries.

Videotaped scans were analyzed at the MESA Ultrasound Reading Center. The baseline carotid scans of the MESA controls served as the comparator scans, and these were reanalyzed at the same time as the ESCAPE-RA scans by a single MESA reader blinded to RA status. Maximal IMT was measured in end-diastole at each of the near and far walls of the right and left CCA, and the anterior oblique, lateral, and posterior oblique views of the bulb-ICA, for a total of 16 IMT measurements per person. The mean maximal IMT of the CCA and bulb-ICA were obtained by averaging the maximal measurements from the near and far walls at each projection, from the right and left sides. When an atherosclerotic plaque was present at the measurement site, it was included in the IMT measurement. The presence of plaque was investigated in the ICA and carotid bulb. Plaque was defined per the Framingham study<sup>27</sup> as focal protrusion into the lumen of the ICA/bulb with reduction in the lumen diameter of more than 25%. For internal carotid IMT measurements, intraobserver coefficient of variation was 6.93%, and interobserver coefficient of variation was 18.8%. For common carotid IMT measurements, intraobserver and interobserver coefficients of variation were 3.48% and 10.7%, respectively<sup>28</sup>.

**Covariate assessment.** ESCAPE RA used the same questionnaires, equipment, methods, and quality control procedures as MESA. Study coordinators were trained and certified by MESA trainers.

**Shared covariates.** Questionnaires were used to collect information on demographics, smoking, and family history. Resting blood pressure (BP) was measured 3 times in the seated position, and the average of the last 2 measurements was used in the analysis. Hypertension was defined by systolic BP > 140 mm Hg, diastolic BP > 90 mm Hg, or antihypertensive medication use. Diabetes was defined as a fasting serum glucose > 126 mg/dl or use of antidiabetic medications. Physical activity was assessed using the MESA activity recall questionnaire. Body mass index (BMI) was calculated as weight (kg) divided by height<sup>2</sup> (m<sup>2</sup>). Prescription and over-the-counter medications used in the preceding 2 weeks were documented from containers supplied by the participant.

**RA-specific covariates.** Forty-four joints in the RA participants were examined by a single trained assessor for swelling, tenderness, deformity, and surgical replacement or fusion. RA disease duration was calculated based on self-report from time of physician diagnosis. RA activity was calculated using the Disease Activity Score for 28 joints (DAS28) with CRP<sup>29</sup>. Functional limitation was assessed with the Stanford Health Assessment Questionnaire (HAQ)<sup>30</sup>. Current and past use of glucocorticoids, biologic and nonbiologic disease modifying agents (DMARD), and nonsteroidal antiinflammatory drugs (NSAID) were ascertained by interviews. Single-view, anterior-posterior radiographs of the hands and feet were obtained

and scored using the Sharp-van der Heijde method<sup>31</sup> by a single, trained radiologist blinded to patient characteristics. For 5 subjects with incomplete radiographic assessments, the missing score (hand or foot) was imputed from available data, based on a regression equation using data from the remaining subjects in the cohort.

**Laboratory covariates.** Fasting sera and plasma were separated by centrifugation and stored at  $-70^{\circ}\text{C}$ . All assays (except RA autoantibodies) were performed at MESA-designated laboratories using MESA quality control procedures. C-reactive protein (CRP), interleukin 6 (IL-6), fibrinogen, homocysteine, soluble intercellular adhesion molecule-1 (sICAM-1), and sE-selectin were measured as described<sup>32</sup>. Low density lipoprotein (LDL) cholesterol was estimated in plasma specimens having a triglyceride value  $< 400$  mg/dl using the Friedewald equation. Positive rheumatoid factor (RF) was defined by a concentration  $> 40$  units, and anticyclic citrullinated peptide (anti-CCP) antibodies by a concentration  $> 60$  units.

HLA alleles bearing the “shared epitope” (SE) were investigated in the RA participants by direct sequencing of a polymerase chain reaction amplicon of exon 2 of the DRB1 gene using Allele SEQR HLA-DRB1 SBT kits (Abbott Molecular, Inc., Des Plaines, IL, USA). Ambiguous typing combinations, e.g., DRB1\*0401/\*0434, were further resolved using intronic reagents flanking exon 2<sup>33</sup>. Capillary sequencing was performed on a 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA) and sequencing data were analyzed with Assign software (Conexio Genomics, Applecross, W. Australia).

**Statistical analysis.** Means and standard deviations for normally distributed and medians and interquartile ranges for non-normally distributed variables were calculated. For categorical variables, counts and percentages were calculated. Differences in continuous variables between RA and control groups were compared using t-tests (for normally distributed variables) or the Kruskal-Wallis test (for non-normally distributed variables). Categorical variables were compared using the chi-square goodness of fit test or Fisher’s exact test.

Multivariate analyses were conducted in participants with complete clinical data ( $n = 393$ ). We included covariates in the multivariate analyses that were unbalanced by exposure status (at the  $p < 0.20$  level) or with strong association with the outcome, in order to account for the potential for residual confounding. Multivariable linear regression models adjusting for age, gender, and race/ethnicity were constructed to estimate adjusted means, 95% confidence intervals, and p values for CV risk factors. Linear regression was used to model the association of RA status with CCA- and bulb-ICA-IMT (as continuous variables). Logistic regression was used to model the association of RA status with plaque. Regression models included adjustments for pertinent demographic and CV risk factors including age, gender, race/ethnic background, highest education level, systolic and diastolic blood pressure (or presence of hypertension), diabetes, ever smoking, high density and LDL cholesterol, triglycerides, use of antihypertensive and lipid-lowering medications, IL-6, CRP, fibrinogen, glucose, amount of weekly intentional exercise, and BMI or waist circumference. Highly skewed variables (e.g., IMT, triglycerides, fibrinogen) were logarithmically transformed. Differences in the associations of CV risk factors with IMT and plaque by RA status were explored using ANCOVA.

Statistical calculations were performed using Intercooled Stata 9 (StataCorp, College Station, TX, USA). In all tests, a 2-tailed  $\alpha$  of 0.05 was defined as the level of statistical significance.

## RESULTS

**Characteristics of RA subjects and MESA controls.** One hundred ninety-six RA patients were recruited to the ESCAPE study and underwent carotid ultrasonography. Of these, 195 had CCA and bulb-ICA images that were suitable for analysis and thus constituted the study population. One hundred ninety-eight MESA controls who had carotid ultrasonography at the baseline visit served as controls; all CCA

and bulb-ICA images were suitable for analysis. The baseline characteristics of the RA and MESA control subjects are presented in Table 1. As expected, due to frequency matching, there were no significant differences in age in the RA versus control group (mean ages 59.4 and 59.8 yrs, respectively), gender (60.2% vs 64.1% female), or proportion of Caucasians (86.2% vs 89.4%). CV risk factors were also balanced, except for modestly higher mean systolic and diastolic blood pressures in the RA participants. As expected, given their underlying inflammatory disorder, RA subjects had significantly higher median CRP, IL-6, fibrinogen, and s-ICAM levels than MESA controls.

Disease-related characteristics of the RA participants have been summarized<sup>24</sup>. Median disease duration was 9 years, and most subjects (78%) were seropositive for either RF or anti-CCP antibodies. About 70% of RA subjects had one or more HLA-DRB1 alleles bearing the SE. The median van der Heijde modified total Sharp score was 44. RA disease activity was low to moderate in most patients, as evidenced by a median DAS28 of 3.57. The majority (93%) of RA subjects were treated with DMARD, including 46% who were receiving biologics either as monotherapy or in combination with a nonbiologic DMARD. About 40% of RA patients were currently treated with glucocorticoids and nearly two-thirds with NSAID.

**Carotid ultrasonographic measures of RA subjects and MESA controls.** The unadjusted mean maximal bulb-ICA-IMT (hereafter referred to as “mean bulb-ICA-IMT”) was significantly higher in the RA group compared to the MESA control group (1.15 vs 1.04 mm, respectively;  $p = 0.002$ ). With adjustment for conventional CV risk factors, the difference in mean bulb-ICA-IMT between the RA and MESA control groups remained significant (1.16 vs 1.02 mm;  $p < 0.001$ ), and was more pronounced for men than women (Figure 1A;  $p$  for heterogeneity = 0.032), and for younger compared to older subjects (Figure 1B;  $p$  for heterogeneity = 0.016). When patients with plaque were excluded from the analysis, the difference in adjusted bulb-ICA-IMT between the RA and control participants remained statistically significant (1.01 vs 0.93 cm;  $p = 0.004$ ). In contrast, neither the unadjusted (0.82 vs 0.84 mm;  $p = 0.25$ ) nor the adjusted (0.83 vs 0.82 mm;  $p = 0.23$ ) CCA-IMT were significantly different between the RA and control groups (data not shown).

The unadjusted prevalence of any plaque was higher in the RA subjects than in controls (21.5% vs 12.1%, respectively;  $p = 0.012$ ; Figure 2). The prevalence odds ratios for carotid plaque for RA versus control subjects according to age group, with adjustment for other demographic and CV risk factors, are summarized in Figure 2. The adjusted odds of plaque was more than doubled in the RA group compared to controls (adjusted OR 2.20, 95% CI 1.21–4.32). The odds ratio was highest in the youngest category (45–54 yrs) and decreased with advancing age ( $p$  for heterogeneity = 0.042).



Table 1. Participant characteristics according to RA status.

Characteristic	RA, n = 195	Controls, n = 198	p
<b>Demographics</b>			
Age, yrs	59.4 ± 8.7	59.8 ± 8.7	0.61
Female, n (%)	118 (60.2)	127 (64.1)	0.42
Caucasian race, n (%)	169 (86.2)	177 (89.4)	0.34
Education, some college or higher, n (%)	147 (75.4)	153 (77.7)	0.59
<b>Cardiovascular risk factors</b>			
Diabetes, n (%)	12 (6.1)	17 (8.6)	0.35
Weight, lbs	176 ± 39	177 ± 38	0.82
BMI	28.4 ± 5.3	28.8 ± 5.7	0.48
<b>Hypertension</b>			
Present, > 140/90, n (%)	54 (27.7)	35 (17.7)	0.018
Systolic BP, mm Hg	128 ± 19	122 ± 19	< 0.001
Diastolic BP, mm Hg	76 ± 9	70 ± 9	< 0.001
Use of antihypertensive medications, n (%)	79 (40.3)	56 (28.3)	0.012
<b>Lipids</b>			
Total cholesterol, mg/dl	195 ± 38	197 ± 36	0.69
LDL cholesterol, mg/dl	116 ± 31	118 ± 30	0.45
HDL cholesterol, mg/dl	55 ± 19	52 ± 14	0.11
Triglycerides, mg/dl	126 ± 92	128 ± 75	0.73
Use of lipid-lowering medications, n (%)	35 (17.9)	46 (23.2)	0.19
<b>Cigarette smoking, n (%)</b>			
Current	23 (11.8)	19 (9.6)	0.49
Ever	115 (59.0)	107 (54.3)	0.35
<b>Serum inflammatory markers</b>			
CRP, mg/l, median (IQR)	2.70 (1.18–7.57)	2.27 (0.92–4.73)	0.011
IL-6, pg/ml, median (IQR)	3.87 (1.77–7.92)	1.12 (0.73–1.89)	< 0.001
Fibrinogen, mg/dl, median (IQR)	335 (279–416)	327 (286–368)	0.039
E-selectin, ng/ml, median (IQR)*	48.6 (29.9–73.2)	47.7 (33.4–56.3)	0.56
s-ICAM-1, ng/ml, median (IQR)*	300 (229–371)	272 (233–307)	0.009

\* E-selectin levels were available in only 24 and s-ICAM levels in only 73 of the controls. BMI: body mass index; BP: blood pressure; LDL/HDL: low/high density lipoprotein; CRP: C-reactive protein; IL-6: interleukin 6; s-ICAM: soluble intercellular adhesion molecule.

Inclusion of IL-6 or CRP in the above models comparing IMT and plaque in the RA and control groups did not statistically significantly change the magnitude of any of the differences between the RA and control groups (data not shown).

*Association of selected risk factors with carotid outcomes according to RA status.* Association of risk factors with carotid outcomes was compared between RA and MESA control participants (Table 2). Those risk factors with the strongest univariate associations with the outcomes, when the RA and non-RA groups were pooled (data not shown), were selected for analysis and included gender, age, hypertension, current smoking, and IL-6. Of note, other inflammation and vascular biomarkers (CRP, fibrinogen, E-selectin, and s-ICAM-1) were not significantly associated with the outcomes in the univariate analyses and therefore were not included in the statistical models. As shown in Table 2, most of the conventional CV risk factors exhibited similar associations with plaque, bulb-ICA-IMT, and CCA-IMT in the 2 groups, except the association of age

with log CCA-IMT, which was modestly stronger in the MESA control group compared to the RA group ( $p$  for heterogeneity = 0.034). Interestingly, log IL-6 was strongly associated with plaque and log bulb-ICA-IMT in the MESA control group ( $\beta$  = 3.77 and 0.11, respectively), but was not associated with these outcomes in the RA group ( $\beta$  = 0.75 and -0.032, respectively;  $p$  for heterogeneity = 0.002 for both CCA-IMT and plaque). Figure 3 illustrates the unadjusted relationship of IL-6 values with bulb-ICA-IMT in the RA versus MESA control groups.

*Association of RA characteristics with carotid plaque and IMT.* The associations of RA characteristics and treatments with carotid plaque and with bulb-ICA-IMT in the RA group are summarized in Tables 3 and 4, respectively. Only HLA-DRB1 SE status was significantly associated with carotid plaque (Table 3). The presence of one or more SE alleles was associated with a near tripling of the adjusted prevalence odds ratio of plaque (OR 2.80, 95% CI 1.07–7.33). No RA characteristics were associated with bulb-ICA-IMT (Table 4).

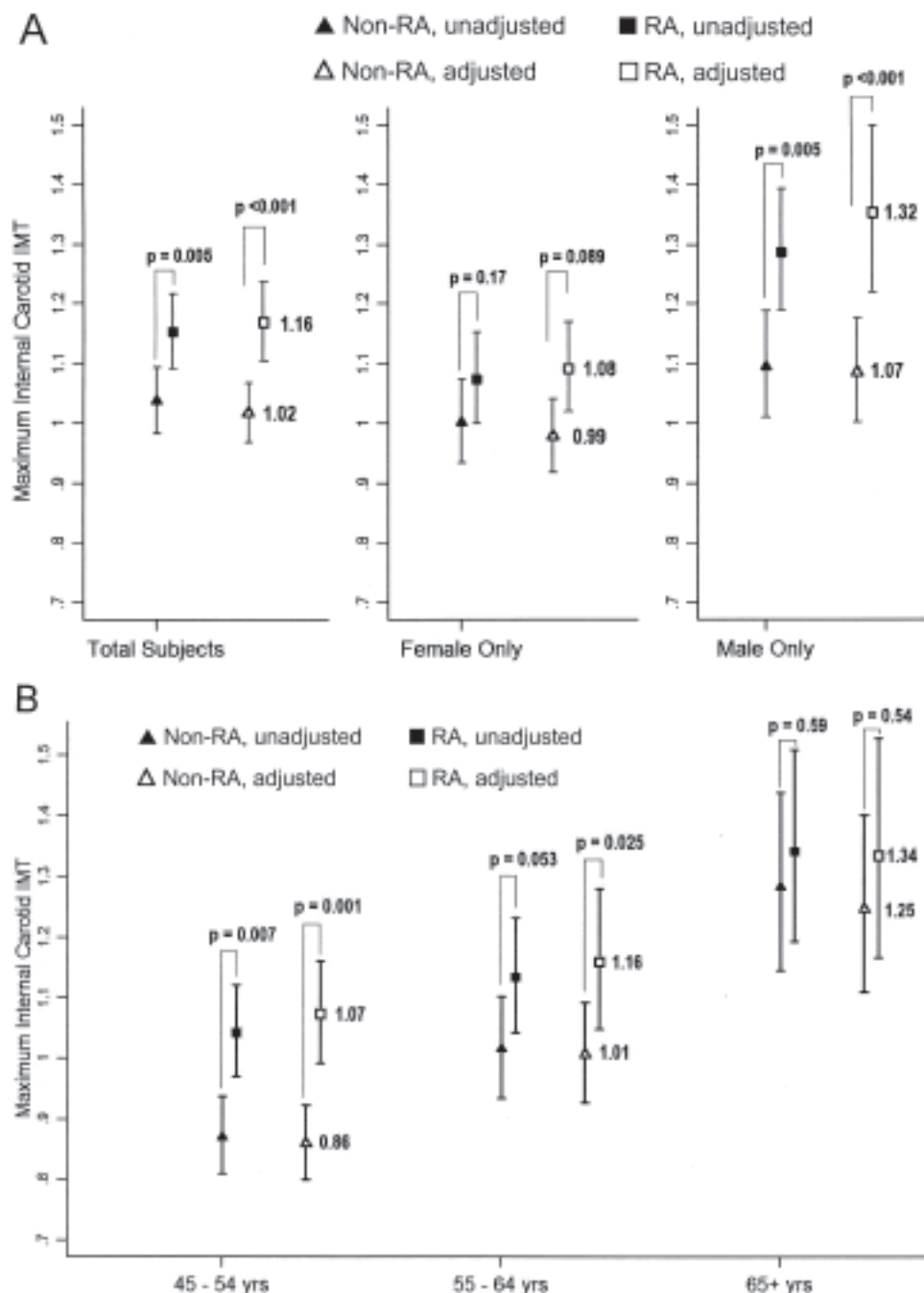


Figure 1. Crude bulb-ICA-IMT values were adjusted for age, race, systolic blood pressure, diastolic blood pressure, anti-hypertensive use, HDL-C, LDL-C, and smoking. Difference in mean bulb-ICA-IMT between RA and control groups was more pronounced for men compared to women (A), and for younger compared to older subjects (B).

## DISCUSSION

Our study demonstrates 3 novel findings: First, mean maximal IMT was higher in the bulb-ICA, but not the CCA, of RA patients compared to non-RA controls. Second, IL-6 (but not other risk factors) was more strongly associated with plaque and bulb-ICA-IMT in the non-RA group than the RA group. Third, in RA patients, the HLA-DRB1 SE was positively correlated with carotid plaque.

A number of previous investigations have reported on IMT and/or plaque prevalence in RA compared to non-RA populations, but with conflicting results<sup>12-22</sup>. The discrepancies in results across these reports may be a result of significant methodological differences, including: (1) variability in excluding prior CV events; (2) inadequate power and/or failure to adjust for multiple conventional CV risk factors; (3) variability in exclusion of plaque from IMT measure-

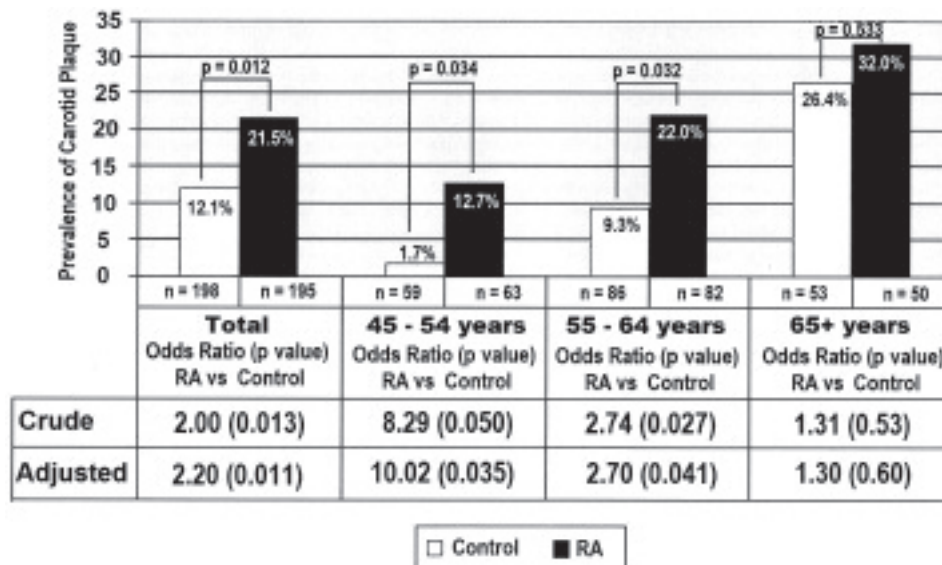


Figure 2. Crude prevalence rates. Prevalence odds ratios (shown in the table) were adjusted for age, gender, race/ethnicity, education, systolic blood pressure, diastolic blood pressure, use of antihypertensives, triglycerides, and smoking. Other covariates tested but not significant in the models included HDL-C, LDL-C, use of lipid-lowering medicines, and diabetes.

Table 2. Adjusted associations of selected risk factors with carotid outcomes according to RA status.

Characteristic*	Any Plaque <sup>§</sup>			Log bulb-ICA-IMT <sup>#</sup>			Log CCA-IMT <sup>#</sup>		
	β-RA	β-MESA	p***	β-RA	β-MESA	p***	β-RA	β-MESA	p***
Male vs female <sup>†</sup>	1.16	1.34	0.83	0.17**	0.11**	0.41	0.11**	0.11**	0.94
Age, per year <sup>††</sup>	1.06**	1.10**	0.41	0.012**	0.013**	0.89	0.005**	0.009**	0.034
Hypertension <sup>†</sup>	1.46	3.36**	0.20	0.024	0.127**	0.17	0.028	0.067**	0.20
Ever vs never smoking <sup>†</sup>	1.76	1.19	0.57	0.13	-0.07	0.071	0.037	-0.039	0.10
Log IL-6, per unit <sup>††</sup>	0.75	3.77**	0.002	-0.032	0.11*	0.002	0.004	0.032**	0.13

\* All models included the characteristic listed in addition to covariates for age, gender, race, highest educational attainment, systolic and diastolic blood pressure, antihypertensive use, HDL and LDL cholesterol, smoking, triglycerides, log IL-6, and use of lipid-lowering medication. \*\*  $p < 0.05$  for association of characteristic with the carotid outcome within groups defined by RA status (RA or MESA control). \*\*\*  $p < 0.05$  indicates significant heterogeneity between RA and control participants in the adjusted association of the characteristic with the carotid outcome. <sup>†</sup>  $\beta$ -coefficients represent difference in carotid outcome between participants with the characteristic vs those without the characteristic. <sup>††</sup>  $\beta$ -coefficients represent change in carotid outcome associated with a one-unit increase in the characteristic. <sup>§</sup> Estimates obtained using multivariable logistic regression;  $\beta$ -coefficients are adjusted odds ratios. <sup>#</sup> Estimates obtained using multivariate linear regression;  $\beta$ -coefficients are adjusted means.

ments; (4) variable definitions of plaque; (5) failure to blind the carotid scan readers; (6) comparison of RA patients to a noncontemporaneous control group; and (7) examination of the CCA only.

The design of our current study provides some advantages over previous reports. The ESCAPE-RA study was modeled closely after MESA, a contemporaneous cohort study of subclinical CV disease in the general population. We utilized MESA ultrasound procedures and risk factor definitions, MESA trained personnel, MESA-designated laboratories, and MESA participants as controls, in order to minimize error in the comparisons of RA to non-RA subjects. In addition, rather than relying on the preexisting analysis of the baseline MESA carotid scans, the MESA

scans were reanalyzed alongside the ESCAPE-RA scans, and in a masked fashion by the same reader. Finally, we performed a systematic evaluation of IMT in both the CCA and ICA.

Our results demonstrate a higher mean maximal bulb-ICA-IMT in the RA subjects compared to MESA controls, even after adjusting for CV risk factors. In contrast, mean maximal CCA-IMT was not significantly different between groups. This may have important clinical implications in RA for future studies. Most carotid ultrasound studies in RA and in the general population have focused on measurement of the CCA. Indeed, increased baseline and increased progression of CCA-IMT in the general population are predictive of myocardial infarction<sup>34-36</sup>. However,

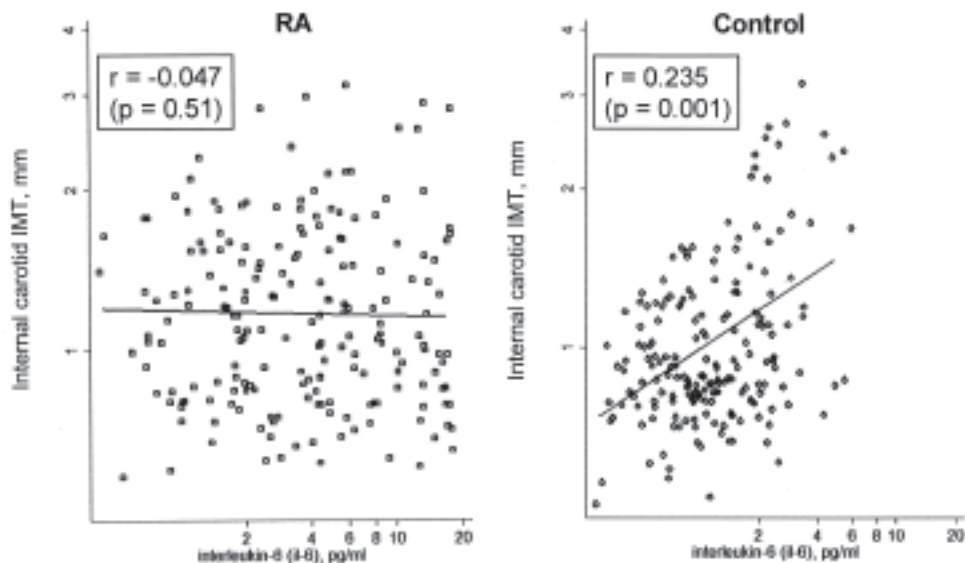


Figure 3. Population average linear trend in maximal internal carotid IMT for each group (solid lines). Axes are logarithmic scale. Spearman correlation coefficients (r) and associated p values for RA and control groups are shown. Correlation of IL-6 with bulb-ICA-IMT in the pooled sample as follows:  $\beta = 0.063$ ,  $p = 0.001$ ; Spearman  $r = 0.165$ ,  $p = 0.001$ .

Table 3. Association of RA characteristics with carotid plaque (maximum carotid stenosis > 25%), n = 195.

Characteristic	Model 1, OR (95% CI)	Model 2, OR (95% CI)
RA duration, per year	1.01 (0.98, 1.04)	0.98 (0.94, 1.02)
Age at RA diagnosis, per year	1.03 (1.00, 1.06)	1.02 (0.98, 1.07)
DAS28-CRP, per unit	1.04 (0.76, 1.43)	1.13 (0.76, 1.67)
Any SE alleles	2.08 (0.90, 4.84)	2.80 (1.07, 7.33)*
Total Sharp score, per unit	1.00 (1.00, 1.01)	1.00 (0.99, 1.00)
HAQ, per unit	1.53 (0.98, 2.39)	1.33 (0.77, 2.31)
Log CRP, per unit	1.00 (0.78, 1.29)	0.82 (0.59, 1.13)
Log IL-6, per unit	0.92 (0.65, 1.32)	0.77 (0.50, 1.19)
Current prednisone use	0.86 (0.42, 1.75)	1.21 (0.51, 2.86)
Cumulative prednisone, per gram	0.99 (0.95, 1.03)	1.00 (0.95, 1.04)
Current nonbiologic DMARD	0.89 (0.35, 2.25)	1.00 (0.34, 2.92)
Current biologic DMARD	0.76 (0.38, 1.51)	0.93 (0.41, 2.10)

\*  $p < 0.05$ . Model 1: crude model, no adjustment. Model 2: adjusted for systolic and diastolic blood pressure, antihypertensive use, HDL-C, LDL-C, use of lipid-lowering medications, diabetes, and ever smoking. DAS28: Disease Activity Score 28; SE: shared epitope; CRP: C-reactive protein; HAQ: Health Assessment Questionnaire; IL-6: interleukin 6; DMARD: disease modifying antirheumatic drug; HDL-C/LDL-C: high/low density lipoprotein cholesterol.

in several<sup>37-39</sup>, but not all<sup>40</sup>, large population cohort studies in which both the bulb-ICA-IMT and CCA-IMT were evaluated, increased baseline and/or change per year in bulb-ICA-IMT conveyed a higher risk than CCA-IMT for incident myocardial infarction. Indeed, the mean change per year in IMT in the Carotid Atherosclerosis Progression Study<sup>23</sup> was more than 30 times greater at the bulb-ICA than

the CCA (0.032 vs 0.001 mm, respectively;  $p < 0.001$ ), and only bulb-ICA-IMT progression correlated strongly with baseline CV risk factors. The higher values and greater variability in measurement of the bulb-ICA compared to the CCA largely reflect greater disease burden in the bulb-ICA; however, because the bulb-ICA is deeper than the CCA, technical challenges may also contribute to greater measurement variability in the bulb-ICA. In addition, the asymmetric nature of atherosclerotic plaque deposition requires sampling in multiple projections in order to decrease measurement variability.

Only 2 other RA studies measured IMT in both the ICA and CCA, but del Rincon, *et al*<sup>21</sup> reported the average of the 2 arteries, rather than individual measurements. Gerli, *et al*<sup>41</sup> measured IMT in 101 RA patients at multiple sites and found higher IMT in the RA patients compared to controls at the carotid bifurcation but not the ICA proper or the CCA, in agreement with our findings since the bifurcation area was included in our bulb-ICA measurement. However, Gerli, *et al*<sup>41</sup> did not statistically adjust for conventional CV risk factors, many of which were present in substantially different frequencies or levels between the groups. Our study indicates a statistically significant increase in bulb-ICA-IMT in the RA compared to the control group, even after adjustment for these risk factors. Whether our finding of a site-specific difference in baseline IMT in RA versus non-RA subjects will translate into different risks of future CV events awaits longterm followup and verification in other RA cohorts. Nonetheless, our data suggest that future studies in RA that utilize carotid artery measurements should include assessment of the bulb-ICA.

Table 4. Association of RA characteristics with log bulb-ICA-IMT, n = 195.

Characteristic	Model 1		Model 2	
	$\beta$ (95% CI)	p	$\beta$ (95% CI)	p
RA duration, per year	0.001 (−0.004, 0.006)	0.65	−0.003 (−0.008, 0.003)	0.33
Age at RA diagnosis, per year	0.006 (0.002, 0.010)	0.007	0.002 (−0.003, 0.008)	0.33
DAS28-CRP	−0.022 (−0.073, 0.029)	0.39	0.005 (−0.044, 0.054)	0.84
Any SE alleles	0.026 (−0.092, 0.144)	0.66	0.020 (−0.088, 0.127)	0.72
Total Sharp score, per 10 units	0.003 (−0.003, 0.010)	0.35	0.002 (−0.004, 0.008)	0.54
HAQ, per unit	0.039 (−0.035, 0.113)	0.30	0.044 (−0.028, 0.116)	0.23
Log CRP	0.002 (−0.039, 0.043)	0.91	−0.026 (−0.065, 0.012)	0.18
Log IL-6	−0.010 (−0.067, 0.047)	0.72	−0.039 (−0.091, 0.014)	0.15
Current prednisone use	−0.100 (−0.211, 0.012)	0.079	−0.056 (−0.161, 0.050)	0.30
Cumulative prednisone	−0.001 (−0.007, 0.004)	0.65	−0.001 (−0.006, 0.004)	0.63
Current nonbiologic DMARD	−0.022 (−0.017, 0.129)	0.78	0.011 (−0.127, 0.150)	0.87
Current biologic DMARD	−0.017 (−0.126, 0.093)	0.76	0.045 (−0.053, 0.145)	0.36

Model 1: crude model, no adjustment. Model 2: adjusted for systolic and diastolic blood pressure, antihypertensive use, HDL-C, LDL-C, use of lipid lowering medications, diabetes, and ever smoking. Definitions: See legend to Table 3.

In addition to higher bulb-ICA-IMT, we also found a higher prevalence of plaque in the carotid arteries of RA patients compared to non-RA controls. This concordance is not surprising, since most plaque occurs in the ICA and bulb, and we included plaque in our IMT measurements. Our observation of increased prevalence of plaque in RA is in agreement with the study by Roman, *et al*<sup>20</sup>. The higher prevalence odds ratio for plaque in our study in the youngest age stratum (45–54 yrs) of the RA versus non-RA groups suggests that RA plays a more significant role, relative to conventional risk factors, in promoting atherosclerosis in younger individuals, while conventional risk factors predominate in older ages, a hypothesis that is also supported by the studies of del Rincon, *et al*<sup>42</sup> and Roman, *et al*<sup>20</sup>.

We compared the association of CV risk factors with carotid artery outcomes in RA versus non-RA participants. The associations of most of the conventional CV risk factors with plaque, CCA-IMT, and bulb-ICA-IMT were of similar strength between the 2 groups. With regard to inflammatory risk factors, only IL-6 levels were associated with plaque and bulb-ICA-IMT, but this relationship was observed only in the control group, an observation that is consistent with a study by Thakore, *et al*<sup>43</sup> in the general population. In individuals without chronic inflammatory diseases, IL-6 levels might be expected to be relatively constant over time, while IL-6 levels in RA are likely to vary widely with changing levels of disease activity and treatments. Although our data are cross-sectional, the associations depicted in Figure 3 indirectly support this notion and may explain the lack of relationship of IL-6 with carotid outcomes in the RA group. In other cross-sectional studies of RA populations, Roman, *et al*<sup>20</sup> also failed to find a relationship of inflammatory or vascular biomarkers (CRP, IL-6, vascular cell adhesion molecule, ICAM-1) with carotid plaque, while del Rincon, *et al*<sup>21</sup> saw a significant correlation of CRP and ESR with both carotid plaque and IMT.

Within the RA group, we also failed to observe a correlation of disease activity with carotid plaque or IMT. Other studies that looked at these variables have reported conflicting results<sup>12–22</sup>. This may be because the risk for accelerated CV disease in RA is established in the preclinical phase, as suggested by Maradit-Kremers, *et al*<sup>6</sup>, who reported a higher rate of myocardial infarction in patients with RA compared to controls prior to the RA diagnosis. The observation by us and others<sup>20,42</sup> that the greatest difference in bulb-ICA-IMT and plaque between RA and controls was in the youngest category of patients further supports this concept.

The HLA-DRB1 SE alleles are highly correlated with the development and severity of RA, as well as with antibodies to citrullinated peptides<sup>44–48</sup>. We observed a strong positive correlation of the presence of one or more copies of the SE with the presence of plaque but not with bulb-ICA-IMT. In other investigations in RA, an association of SE with impaired endothelium-dependent vasodilation<sup>49</sup> and with CV-associated death<sup>50–52</sup> were reported. Two recent genome-wide analyses of atherosclerosis in the general population did not reveal a signal in the MHC region<sup>53,54</sup>. Thus, this genetic predisposition to accelerated atherosclerosis may be unique to RA.

The association of HLA-DRB1 with RA disease susceptibility appears to be explained in large part by its association with anti-CCP antibodies and, to a lesser extent, with RF. Surprisingly, however, RF and anti-CCP antibodies were not correlated in our study with plaque or bulb-ICA-IMT. These results differ from those of Gerli, *et al*<sup>41</sup>, who reported an association between anti-CCP antibody and ICA-IMT. Studies in larger patient populations will be needed to elucidate the potential independent contributions of RA-specific autoantibodies and RA susceptibility genes in promoting or inhibiting atherosclerosis.

Some limitations of our study merit mention. First, we



applied DMARD use as a means of excluding MESA control participants with RA. This method is more reliable than patient self-report of diagnosis of RA and is commonly used in epidemiological studies<sup>55</sup>; however, we cannot exclude the possibility that we included some RA patients not currently taking DMARD. A second potential limitation relates to differences in referral patterns into the study (clinic-based for ESCAPE-RA vs community-based for MESA), which may have introduced selection bias. However, as the 2 cohorts were geographically compatible, it is likely that any bias related to selection would be limited in extent. Third, our analyses were cross-sectional and thus temporality cannot be determined. Finally, we measured a surrogate of CV disease rather than clinical CV events; nonetheless, both carotid plaque and IMT are well validated independent predictors of future stroke and myocardial infarction in the general population.

We observed a greater prevalence of plaque and greater IMT in the bulb-ICA but not the CCA of RA patients compared to non-RA controls, even after adjusting for conventional CV risk factors and other potential confounders. SE alleles appeared to convey risk for more severe atherosclerosis within the RA group. The role for vascular imaging in risk prediction for future CV events in RA is not yet clear. For now, aggressive management of both RA and conventional CV risk factors — in an attempt to limit future CV events — is prudent.

## ACKNOWLEDGMENT

We are indebted to the ESCAPE RA Staff, Marilyn Towns, Michelle Jones, Patricia Jones, Marissa Hildebrandt, and Shawn Francowiak, and to the staffs of the Johns Hopkins Bayview Medical Center General Clinical Research Center and the field center of the Baltimore MESA cohort and the MESA Coordinating Center at the University of Washington, Seattle. We are also indebted to the ESCAPE and MESA participants for the generous donation of their time and interest. Drs. Uzma Haque, Clifton Bingham III, Carol Ziminski, Jill Ratain, Ira Fine, Joyce Kopicky-Burd, David McGinnis, Andrea Marx, Howard Hauptman, Achini Perera, Peter Holt, Alan Matsumoto, Megan Clowse, Gordon Lam and others generously recommended their patients for this study.

## REFERENCES

- Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE, et al. Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 2003;107:1303-7.
- Wolfe F, Freundlich B, Straus WL. Increase in cardiovascular and cerebrovascular disease prevalence in rheumatoid arthritis. *J Rheumatol* 2003;30:36-40.
- Goodson N, Symmons D. Rheumatoid arthritis in women: still associated with an increased mortality. *Ann Rheum Dis* 2002;61:955-6.
- Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. *Arthritis Rheum* 2005;52:722-32.
- del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001;44:2737-45.
- Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum* 2005;52:402-11.
- Hodis HN, Mack WJ, LaBree L, Selzer RH, Liu CR, Liu CH, et al. The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med* 1998;128:262-9.
- Kawamori R, Yamasaki Y, Matsushima H, Nishizawa H, Nao K, Hougaku H, et al. Prevalence of carotid atherosclerosis in diabetic patients. Ultrasound high-resolution B-mode imaging on carotid arteries. *Diabetes Care* 1992;15:1290-4.
- Lorenz MW, von Kegler S, Steinmetz H, Markus HS, Sitzer M. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). *Stroke* 2006;37:87-92.
- Longstreth WT Jr, Shemanski L, Lefkowitz D, O'Leary DH, Polak JF, Wolfson SK Jr. Asymptomatic internal carotid artery stenosis defined by ultrasound and the risk of subsequent stroke in the elderly. The Cardiovascular Health Study. *Stroke* 1998;29:2371-6.
- Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. *J Am Soc Echocardiogr* 2008;21:93-111.
- Jonsson SW, Backman C, Johnson O, Karp K, Lundstrom E, Sundqvist KG, et al. Increased prevalence of atherosclerosis in patients with medium term rheumatoid arthritis. *J Rheumatol* 2001;28:2597-602.
- Kumeda Y, Inaba M, Goto H, Nagata M, Henmi Y, Furumitsu Y, et al. Increased thickness of the arterial intima-media detected by ultrasonography in patients with rheumatoid arthritis. *Arthritis Rheum* 2002;46:1489-97.
- Park YB, Ahn CW, Choi HK, Lee SH, In BH, Lee HC, et al. Atherosclerosis in rheumatoid arthritis: morphologic evidence obtained by carotid ultrasound. *Arthritis Rheum* 2002;46:1714-9.
- Gonzalez-Juanatey C, Llorca J, Testa A, Revuelta J, Garcia-Porrua C, Gonzalez-Gay MA. Increased prevalence of severe subclinical atherosclerotic findings in long-term treated rheumatoid arthritis patients without clinically evident atherosclerotic disease. *Medicine (Baltimore)* 2003;82:407-13.
- Alkaabi JK, Ho M, Levison R, Pullar T, Belch JJ. Rheumatoid arthritis and macrovascular disease. *Rheumatology (Oxford)* 2003;42:292-7.
- Grover S, Sinha RP, Singh U, Tewari S, Aggarwal A, Misra R. Subclinical atherosclerosis in rheumatoid arthritis in India. *J Rheumatol* 2006;33:244-7.
- Daza L, Aguirre M, Jimenez M, Herrera R, Bollain JJ. Common carotid intima-media thickness and von Willebrand factor serum levels in rheumatoid arthritis female patients without cardiovascular risk factors. *Clin Rheumatol* 2007;26:533-7.
- Hannawi S, Haluska B, Marwick TH, Thomas R. Atherosclerotic disease is increased in recent-onset rheumatoid arthritis: a critical role for inflammation. *Arthritis Res Ther* 2007;96:R116.
- Roman MJ, Moeller E, Davis A, Paget SA, Crow MK, Lockshin MD, et al. Preclinical carotid atherosclerosis in patients with rheumatoid arthritis. *Ann Intern Med* 2006;144:249-56.
- del Rincon I, Williams K, Stern MP, Freeman GL, O'Leary DH, Escalante A. Association between carotid atherosclerosis and markers of inflammation in rheumatoid arthritis patients and healthy subjects. *Arthritis Rheum* 2003;48:1833-40.
- Gerli R, Sherer Y, Vaudo G, Schillaci G, Gilburd B, Giordano A, et al. Early atherosclerosis in rheumatoid arthritis: effects of smoking on thickness of the carotid artery intima media. *Ann NY Acad Sci* 2005;1051:281-90.

23. Mackinnon AD, Jerrard-Dunne P, Sitzer M, Buehler A, von Kegler S, Markus HS. Rates and determinants of site-specific progression of carotid artery intima-media thickness: the carotid atherosclerosis progression study. *Stroke* 2004;35:2150-4.
24. Giles JT, Szklo M, Post W, Petri M, Blumenthal RS, Lam G, et al. Coronary arterial calcification in rheumatoid arthritis: comparison with the Multi-Ethnic Study of Atherosclerosis. *Arthritis Res Ther* 2009;11:R36.
25. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.
26. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, et al. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol* 2002;156:871-81.
27. Wilson PW, Hoeg JM, D'Agostino RB, Silbershatz H, Belanger AM, Poehlmann H, et al. Cumulative effects of high cholesterol levels, high blood pressure, and cigarette smoking on carotid stenosis. *N Engl J Med* 1997;337:516-22.
28. Bui AL, Katz R, Kestenbaum B, de Boer IH, Fried LF, Polak JF, et al. Cystatin C and carotid intima-media thickness in asymptomatic adults: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Kidney Dis* 2009;53:389-98.
29. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995;38:44-8.
30. Wolfe F, Kleinheksel SM, Cathey MA, Hawley DJ, Spitz PW, Fries JF. The clinical value of the Stanford Health Assessment Questionnaire Functional Disability Index in patients with rheumatoid arthritis. *J Rheumatol* 1988;15:1480-8.
31. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. *J Rheumatol* 2000;27:261-3.
32. Nettleton JA, Steffen LM, Mayer-Davis EJ, Jenny NS, Jiang R, Herrington DM, et al. Dietary patterns are associated with biochemical markers of inflammation and endothelial activation in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Clin Nutr* 2006;83:1369-79.
33. Kotsch K, Wehling J, Blasczyk R. Sequencing of HLA class II genes based on the conserved diversity of the non-coding regions: sequencing based typing of HLA-DRB genes. *Tissue Antigens* 1999;53:486-97.
34. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. *Am J Epidemiol* 1997;146:483-94.
35. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. *Arterioscler Thromb* 1991;11:1245-9.
36. Salonen JT, Salonen R. Ultrasound B-mode imaging in observational studies of atherosclerotic progression. *Circulation* 1993;87 Suppl:II56-II65.
37. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med* 1999;340:14-22.
38. Wagenknecht LE, Zaccaro D, Espeland MA, Karter AJ, O'Leary DH, Haffner SM. Diabetes and progression of carotid atherosclerosis: the insulin resistance atherosclerosis study. *Arterioscler Thromb Vasc Biol* 2003;23:1035-41.
39. Lynch J, Kaplan GA, Salonen R, Salonen JT. Socioeconomic status and progression of carotid atherosclerosis. Prospective evidence from the Kuopio Ischemic Heart Disease Risk Factor Study. *Arterioscler Thromb Vasc Biol* 1997;17:513-9.
40. Li R, Duncan BB, Metcalf PA, Crouse JR III, Sharrett AR, Tyroler HA, et al. B-mode-detected carotid artery plaque in a general population. Atherosclerosis Risk in Communities (ARIC) Study Investigators. *Stroke* 1994;25:2377-83.
41. Gerli R, Bartoloni BE, Sherer Y, Vaudo G, Moscatelli S, Shoenfeld Y. Association of anti-cyclic citrullinated peptide antibodies with subclinical atherosclerosis in patients with rheumatoid arthritis. *Ann Rheum Dis* 2008;67:724-5.
42. del Rincon I, Freeman GL, Haas RW, O'Leary DH, Escalante A. Relative contribution of cardiovascular risk factors and rheumatoid arthritis clinical manifestations to atherosclerosis. *Arthritis Rheum* 2005;52:3413-23.
43. Thakore AH, Guo CY, Larson MG, Corey D, Wang TJ, Vasan RS, et al. Association of multiple inflammatory markers with carotid intimal medial thickness and stenosis (from the Framingham Heart Study). *Am J Cardiol* 2007;99:1598-602.
44. Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis. An approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis Rheum* 1987;30:1205-13.
45. du Montcel ST, Michou L, Petit-Teixeira E, Osorio J, Lemaire I, Lasbleiz S, et al. New classification of HLA-DRB1 alleles supports the shared epitope hypothesis of rheumatoid arthritis susceptibility. *Arthritis Rheum* 2005;52:1063-8.
46. Gorman JD, Lum RF, Chen JJ, Suarez-Almazor ME, Thomson G, Criswell LA. Impact of shared epitope genotype and ethnicity on erosive disease: a meta-analysis of 3,240 rheumatoid arthritis patients. *Arthritis Rheum* 2004;50:400-12.
47. Auger I, Sebbag M, Vincent C, Balandraud N, Guis S, Nogueira L, et al. Influence of HLA-DR genes on the production of rheumatoid arthritis-specific autoantibodies to citrullinated fibrinogen. *Arthritis Rheum* 2005;52:3424-32.
48. van Gaalen FA, van Aken J, Huizinga TW, Schreuder GM, Breedveld FC, Zanelli E, et al. Association between HLA class II genes and autoantibodies to cyclic citrullinated peptides (CCPs) influences the severity of rheumatoid arthritis. *Arthritis Rheum* 2004;50:2113-21.
49. Gonzalez-Gay MA, Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Martin J, Llorca J. Endothelial dysfunction, carotid intima-media thickness, and accelerated atherosclerosis in rheumatoid arthritis. *Semin Arthritis Rheum* 2008;38:67-70.
50. Matvey DL, Thomson W, Ollier WE, Batley M, Davies PG, Gough AK, et al. Association of DRB1 shared epitope genotypes with early mortality in rheumatoid arthritis: results of eighteen years of followup from the early rheumatoid arthritis study. *Arthritis Rheum* 2007;56:1408-16.
51. Farragher TM, Goodson NJ, Naseem H, Silman AJ, Thomson W, Symmons D, et al. Association of the HLA-DRB1 gene with premature death, particularly from cardiovascular disease, in patients with rheumatoid arthritis and inflammatory polyarthritis. *Arthritis Rheum* 2008;58:359-69.
52. Gonzalez-Gay MA, Gonzalez-Juanatey C, Lopez-Diaz MJ, Pineiro A, Garcia-Porrua C, Miranda-Filloo JA, et al. HLA-DRB1 and persistent chronic inflammation contribute to cardiovascular events and cardiovascular mortality in patients with rheumatoid arthritis. *Arthritis Rheum* 2007;57:125-32.
53. Samani NJ, Erdmann J, Hall AS, Hengstenberg C, Mangino M, Mayer B, et al. Genomewide association analysis of coronary artery disease. *N Engl J Med* 2007;357:443-53.
54. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* 2007;447:661-78.
55. Ling SM, Fried LP, Garrett E, Hirsch R, Guralnik JM, Hochberg MC. The accuracy of self-report of physician diagnosed rheumatoid arthritis in moderately to severely disabled older women. Women's Health and Aging Collaborative Research Group. *J Rheumatol* 2000;27:1390-4.