Carotid Plaque Characteristics and Disease Activity in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Carotid plaques (CP) are predictive of acute coronary syndrome in patients with rheumatoid arthritis (RA), suggesting that atherosclerotic plaques in these patients are vulnerable. The objective of our study was to characterize vulnerability of CP in patients with RA compared to a control population, and between RA patients with different levels of disease activity.

Methods. Ultrasound examination of carotid arteries was performed in 152 patients with RA and 89 controls. CP echolucency was evaluated by the Gray-Scale Median (GSM) technique. Lower GSM values indicate higher vulnerability of plaques. CP characteristics were compared between RA patients with active disease and in remission, and between patients and controls. All analyses were performed with adjustment for confounding factors (sex, age, smoking, and blood pressure). Poisson regression analysis was used for count data, mixed modeling for GSM and area per plaque, and analysis of covariance for minimum GSM value per patient.

Results. Patients with RA more frequently had CP (median 2, range 0, 4) compared with controls (median 1, range 0, 3; $p < 0.001$), after adjustment for age and sex. Patients with active RA disease according to the Clinical Disease Activity Index (CDAI) had lower median GSM ($p = 0.03$), minimum GSM ($p = 0.03$), and a larger CP area (although the latter finding was not significant; $p = 0.27$), compared with patients with RA in remission. These findings were not confirmed for other disease measures (Simplified Disease Activity Index, Disease Activity Score-28, C-reactive protein, erythrocyte sedimentation rate).

Conclusion. Patients with RA had more CP compared with controls and patients in CDAI remission, and controls had more stable CP than patients with active disease; these findings point to the importance of achieving remission in RA. (J Rheumatol First Release Jan 15 2013; J Rheumatol 2013;40:359–68; doi:10.3899/jrheum.120621)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ATHEROSCLEROSIS CAROTID PLAQUE
CARDIOVASCULAR DISEASE GRAY-SCALE MEDIAN

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Dr. Semb has received speaker's honoraria and/or consulting fees from Merck/Schering-Plough, Abbott, BMS, Pfizer, and Roche. J. Hisdal has received speaker's honoraria from Pfizer. Dr. Provan has received speaker's honoraria from Abbott, BMS, and Roche. Dr. Kvien has received speaker's and/or consulting honoraria and/or research grants from Abbott, BMS, Merck/Schering-Plough, Pfizer, Roche, UCB, and Wyeth. E. Stranden has received speaker's honoraria from Pfizer, 3M, and Meda and university sponsorship from Hoechts.

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Accepted for publication November 19, 2012.

The presence of carotid artery plaques (CP) in the general population is closely related to future cardiovascular (CV) outcome[1]. Moreover, the composition of the plaque is important and a CV event follows plaque rupture. The vulnerable atherosclerotic plaque is characterized by a thin fibrous cap, a larger lipid core, less collagen, ulceration, noncalcification, intraplaque hemorrhage, and infiltration of inflammatory cells[2]. Assessment of plaque vulnerability has been performed using ultrasound techniques and presented as CP echolucency and area[3,4]. The relationship of plaque vulnerability to Gray-Scale Median (GSM) has been described by el-Barghouty, *et al*[5,6] and others. Specifically, high lipid and hemorrhagic content of the CP, as established histologically, had a low GSM, whereas plaques with high fibrous content had a high GSM[5,6]. Studies confirm that the presence of CP and its echolucency as evaluated by the GSM method predict outcomes. Lower GSM of CP was associated with positive computed tomography (CT) scans for cerebral stroke, compared to negative CT scans for stroke with higher GSM values[7]. In another study, the GSM

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of symptomatic CP was lower than that of asymptomatic CP[5]. Madycki and coworkers showed that the risk of cerebral microembolism after carotid surgery was increased with the decrease of CP echodensity evaluated by GSM[4]. Hypoechoic plaques were associated with an increased risk of stroke in the Cardiovascular Health Study: 4886 persons were followed for an average of 3.3 years[8]. This finding was confirmed in several other prospective studies[9,10]. Thus, echolucency is recognized as an important factor in determining risk for future neurologic events[11,12]. Further, CP echolucency and size have been shown to predict CV disease in the general population[9,13]. In a recent publication, 574 patients with asymptomatic CP were followed with ultrasound examinations of the carotids for 6 and 9 months; echolucency evaluated by ultrasound and GSM was an indicator for plaque instability and identified patients at risk for major adverse CV events, in that increasing echolucency was predictive of CV outcome[14]. Moreover, plaque vulnerability or instability may not be merely a local vascular occurrence, but reflect a generalized phenomenon, and it may exist simultaneously at multiple sites in the vascular bed[15]. Therefore, the state of a CP may relate to status of plaques in other arteries. Hence, it may be of importance to evaluate both the size and the composition of CP.

Patients with rheumatoid arthritis (RA) have 2–3 times more atherosclerotic plaques in the carotid artery compared with the general population[16,17]. Limited data are available on atherosclerotic plaque composition in patients with RA. The features of coronary atherosclerotic plaques were examined postmortem in a small study that indicated that patients with RA had less coronary atherosclerosis (fewer plaques and stenoses) than controls, but a higher number of vulnerable plaques and a higher content of inflammatory components in the main coronary arteries, compared with non-RA patients[18]. A recent prospective report in 599 RA patients without previous CV disease confirmed that both carotid intima-media thickness (IMT) and the presence of CP independently predicted future acute coronary syndromes[19]. The incidence of new acute coronary syndromes was 2.3-fold and 4-fold higher for unilateral and bilateral CP, respectively, compared to patients without CP. These findings indicate an association between the characteristics of carotid and coronary atherosclerotic plaques. A possible explanation for the increased incidence of coronary events in patients with CP is that patients with RA have numerically more atherosclerotic plaques and thus have a higher risk for CV events. Another pathogenic possibility is that atherosclerotic plaques have higher vulnerability for rupture in patients with RA, compared with cases without RA.

These findings indicate the need for analyses of plaque composition and plaque vulnerability in RA. The aim of our study was to evaluate the number of CP and compare ultrasonic CP characteristics between RA patients with different levels of disease activity, and to compare RA patients with population controls.

MATERIALS AND METHODS

Population. Patients with RA (n = 152), diagnosed according to the 1987 American College of Rheumatology criteria[20], were identified from the 10-year followup of the Oslo RA register (n = 45) and the 15-year followup of the EURIDISS cohort (n = 107). Details about these cohorts and followup examinations have been published[21,22].

Two hundred community control subjects were selected by the Statistics Norway database to match the RA patient cohort for sex, age, and residential area. Individuals with a history of inflammatory joint disease were excluded. Patients and controls received a letter with an invitation to participate in the study. While 57.0% of the surviving participants of the EURIDISS and Oslo RA register cohorts agreed to participate in the 15- and 10-year followup examination, the participation rate of the population controls was 43.5%.

The protocol was approved by the Norwegian Regional Committee for Research Ethics and the participants signed an informed consent.

RA disease activity. A trained study nurse, who was blinded to the CV risk profile of the patients, assessed the number of swollen and tender joints (28-joint counts). Disease activity was assessed by the Clinical Disease Activity Index (CDAI) as the sum of the number of swollen joints (SJC) plus the number of tender joints (TJC) plus patient global visual analog scale (VAS; cm) plus investigator global VAS (cm), and used in the analyses with an approach similar to that used by Provan, *et al*[23]. We also calculated the Simplified Disease Activity Index [(SDAI); TJC28 + SJC28 + VAS physician (cm) + VAS patient (cm)] and Disease Activity Score-28 [(DAS28; 0.56 √(TJC28) + 0.28 √(SJC28) + 0.36ln (CRP [mg/l] + 1) + 0.014 (VAS patient [cm]) + 0.96]. The cutoff values for remission, low disease activity, and moderate and high disease activity as described by Klarenbeek, *et al* are shown in Table 2[24]. Not all components of the composite scores were available in all patients (n = 7), and the numbers of patients with computed CDAI, SDAI, and DAS28 are given in Table 2.

Carotid ultrasound. Bilateral B-mode ultrasonographic examinations of the carotid arteries were performed with a GE Vivid-7 scanner (GE Vingmed Ultrasound) using a 12 (9–14) MHz linear matrix array transducer. An experienced sonographer performed all the examinations. Representative images were stored and sent to a reader panel; readers were blinded to disease activity.

IMT measurements were performed bilaterally in the far wall of the common carotid artery (CCA) over a 5-mm segment, from about 15 to 10 mm proximal to the start of the carotid bulb. Before an image was stored for analysis, we ensured that both the near wall and far wall were visualized with sharp edges, indicating an isonation of about 90° to the vessel wall, to avoid overestimation of IMT and plaque size. IMT measurements were read offline by 2 experienced vascular physiologists (ES and JH) from JPEG images using AMS analysis software (Artery Measurement System; T. Gustavsson)[25,26]. Each 5-mm section generated about 50 IMT calculations, and median values were used as the best estimate on an individual level for further analyses. The correlation of IMT values between the 2 readers was good, with an intraclass correlation coefficient (ICC) of 0.985 (95% CI 0.975–0.991).

Atherosclerotic plaques in the CCA, carotid artery bulb, and the internal carotid artery (ICA) were identified bilaterally in the longitudinal view when both IMT observations of far wall and near wall had sharp edges as protrusions into the lumen ≥ 1.5 mm. In cases of doubt about the presence of a plaque, it was verified by a cross-sectional image obtained by rotating the probe 90°. Plaque echolucency and area were analyzed only if a sharp delineation of the plaque was obtained.

Analysis of the area and plaque morphology was performed offline by the same physiologists. The plaque area was calculated by delineating the plaque contour image normalization, and digital standardization of plaque morphology was done using the GSM technique. The median value for echolucency of plaques of each individual was used in these analyses, and the lowest GSM measured in a CP per patient was denoted the minimum GSM[25,27,28]. The ICC between the 2 readers for GSM was 0.990 (95% CI 0.977–0.996) and for plaque area was 0.955 (95% CI 0.898–0.980).

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Soluble biomarkers. Patients and control subjects fasted 3 h before blood samples were taken. Soluble biomarkers were examined consecutively: erythrocyte sedimentation rate (ESR) by the Westergren method, C-reactive protein (CRP), total cholesterol, high-density lipoprotein cholesterol, and triglycerides by COBAS 6000 (Roche Diagnostics). Low-density lipoprotein cholesterol was calculated by Friedewald's formula. Other biological markers were analyzed in batches from frozen serum or plasma. Anti-cyclic citrullinated peptide (anti-CCP) antibodies and IgM rheumatoid factor (RF) were determined by ELISA (Inova Diagnostics).

Statistics. Demographic characteristics of patients with RA and controls are presented as crude data and results are expressed as mean ± SD and median (interquartile range; IQR) for normally and non-normally distributed characteristics, respectively. Skewed variables were log-transformed for comparisons. The data were compared using analysis of covariance (ANCOVA) and logistic or Poisson regression adjusted for age and sex as appropriate.

Different methods were used to compare patients and controls and to examine trends within levels of RA disease activity: Poisson regression for comparison of the number of plaques per person, mixed models with a random intercept to compare the plaque area and GSM (this method was selected because the maximum number of plaques per person was 4), and an ANCOVA model was used for comparative analyses of minimum GSM. Trend analyses were performed by linear contrasts within each model to determine relationships to disease activity. Because of the low number of subjects with plaques and to avoid overfitting the models, we restricted the number of adjustment factors to 4 (in addition to the RA/control groups). We chose to adjust for blood pressure and smoking (in addition to age and sex) because they are important risk factors carrying a high risk for future myocardial infarction. Risk factors such as diabetes, body mass index, familial CV disease, and others were therefore excluded from the list of adjustment factors because of parsimony of the model. In particular, diabetes was excluded because this disease was present in only 8 patients with RA and in 2 control persons. Two-tailed p values are reported; $p < 0.05$ was considered significant. Data analyses were performed using IBM SPSS v19 and SAS v9.2.

RESULTS

Characteristics of patients with RA and control subjects. Patients with RA (n = 152) had median disease duration of 17 years (IQR 15–19) and were older, more often female, and had higher blood pressure and more often diabetes compared with the controls (n = 89; Table 1). Further, patients with RA had a larger IMT value compared to controls, while controls had a higher prevalence of known CV disease. The median disease activity data for CDAI, SDAI, and DAS28 are also shown in Table 1.

The distribution of patients across the disease activity categories of CDAI and SDAI was comparable, while nearly twice as many patients were in remission when disease activity was measured by DAS28 (Table 2). Patient characteristics across disease activity categories are also presented in Table 2 (crude data). In general, traditional CV risk factors were similar across the various disease activity categories, but atherogenic lipid levels were lower with increasing disease activity in CDAI and SDAI, but not in DAS28 (Table 2).

Plaque characteristics. CP was twice as common in patients with RA (90/152; 59.2%) compared to controls (24/89; 27.0%; Table 1). The 90 RA patients with CP had a total number of 183 CP compared to 24 controls with 33 CP. Thus, patients with RA had CP more often, and when present, CP were also more numerous (Figure 1, Appendix 1). This difference was robust and remained significant after adjustments for age, sex, smoking, and blood pressure (Figure 2). CP was also more often present bilaterally in RA compared to controls [RA 26/90 (28.8%), controls 4/24 (16.6%)], but was localized predominantly in the carotid bulb and ICA in both RA (74.2%) and in controls (90.9%).

Number of CP was not associated with levels of RA disease activity ($p = 0.65$; Appendix 1), sex ($p = 0.36$), blood pressure ($p = 0.23$), smoking ($p = 0.97$), or disease duration ($p = 0.81$), but was associated with age ($p = 0.02$).

CP characteristics were compared between RA patients and controls, and within patients with RA according to levels of disease activity as measured by CDAI, SDAI, and DAS28. A significant trend association (inverse relationship) was observed between disease activity according to CDAI and both mean GSM ($p = 0.03$) and minimum GSM ($p = 0.03$; Figure 2, Appendix 2). This trend was similar but was not significant for SDAI, and was not observed for the DAS28. Because of differences in the disease activity indexing, the estimates for the control group differ slightly in the analyses. This does not reflect disease activity in the control group.

There was no difference between the GSM at the various localizations (ICA, carotid bulb, and CCA) between patients with RA and controls (data not shown).

Disease activity was not associated with plaque area in patients with RA (Figure 2, Appendix 2), and there was no significant difference between RA patients and controls regarding plaque area.

DISCUSSION

The main focus of our study was to evaluate the vulnerability of CP in patients with RA. To our knowledge, this is not well characterized in these patients, although 1 study has reported lower GSM of CP[29]. Our findings indicate that patients with active RA disease (according to CDAI) had lower median GSM and minimum GSM, suggesting more stable plaques, compared with patients with RA in remission, and pointing to the importance of remission. This association was not found for other disease measures. Our study also confirms that patients with RA have a larger burden of carotid artery atherosclerosis compared to controls, because they have a higher prevalence of and a significantly higher number of CP[16,30].

The reasons for the inconsistent findings across the various disease activity measures regarding CP GSM and area are not known. SDAI and DAS28 include the inflammatory measures CRP and ESR, which may reflect disease activity at a single timepoint rather than the longer time period necessary to deposit an atherosclerotic CP. Building a CP is a process taking several years and thus CDAI, which does not include the inflammatory variables CRP or ESR,

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Table 1. Characteristics of patients with rheumatoid arthritis (RA) and controls.

Characteristic	RA, n = 152	Controls, n = 89	p
Age, yrs, median (IQR)	62.7 (53.6, 71.2)	55.7 (44.3, 63.1)	< 0.001*
Sex female, n (%)	116 (76.3)	54 (60.7)	0.01
Cardiovascular risk factors			
Smoking (ever), n (%)	97 (63.8)	56 (62.9)	0.94
Systolic blood pressure, mm Hg	134.5 ± 20.1	124.8 ± 18.1	0.07
Diastolic blood pressure, mm Hg	80.5 ± 9.6	76.4 ± 10.5	0.14
Diabetes, n (%)	14 (9.2)	2 (2.2)	0.12
Body mass index, kg/m^2	25.9 ± 5.0	25.4 ± 4.0	0.25
Waist circumference, cm	88.4 ± 14.1	86.8 ± 12.7	0.15
Familial cardiovascular disease, n (%)	19 (12.5)	19 (21.3)	0.08
Cardiovascular disease markers			
Intima-media thickness, mm	0.8 ± 0.2	0.7 ± 0.2	0.39
Patients with carotid plaque, n (%)	90 (59.2)	24 (27.0)	< 0.001
No. carotid plaques, median (IQR)	1 (0, 2)	0 (0, 1)	< 0.001
Area of carotid plaques, mm^2	16.5 ± 8.1	17.3 + 10.9	0.77
Gray-Scale Median value	89.3 ± 28.1	102.6 + 23.1	0.12
Lipids			
Total cholesterol, mmol/l	5.7 ± 1.2	5.8 + 1.0	0.009
HDL cholesterol, mmol/l	1.8 ± 0.6	1.7 ± 0.5	0.11
Triglycerides, mmol/l, median (IQR)	1.1 (0.8, 1.5)	1.0 (0.8, 1.5)	0.43
LDL cholesterol, mmol/l	3.3 ± 1.1	3.5 ± 0.9	0.02
Inflammatory markers, median (IQR)			
ESR, mm/h	13.0 (7.3, 21.8)	8.0 (6.0, 15.0)	0.21
CRP, mg/l	4.0 (1.0, 8.0)	1.0 (1.0, 2.0)	< 0.001
Medication use, n (%)			
Statins	27 (17.8)	13 (14.6)	0.74
Hypertension medications	56 (36.8)	18 (20.2)	0.40
DMARD	100 (65.85)		
Tumor necrosis factor inhibitors	32 (21.1)		
Prednisolone	51 (33.6)		
Methotrexate	50 (32.9)		
Disease characteristics			
Disease duration, yrs, median (IQR)	17 (15, 19)		
Rheumatoid factor-positive, n (%)	77 (50.7)		
ACPA-positive, n (%)	75 (49.3)		
28 Tender joint count	2.3 ± 3.9		
28 Swollen joint count	1.9 ± 2.7		
Physician VAS, cm	2.5 ± 1.6		
Patient VAS, cm	3.3 ± 2.3		
DAS28	2.6 ± 1.0		
CDAI	6.9 ± 6.9		
SDAI	7.7 ± 7.3		

Data are means ± SD unless stated otherwise. P values are adjusted for age and sex using analysis of covariance (continuous variables), logistic regression for dichotomous variables, and Poisson regression for counts. Values for erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and triglycerides were log-transformed for p value calculation. * Mann-Whitney U test (unadjusted). DMARD: disease-modifying antirheumatic drugs; ACPA: anticitrullinated protein antibodies; VAS: visual analog scale for disease activity; DAS:28: Disease Activity Score based on 28-joint count; IQR: interquartile range; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index.

may therefore better reflect CP characteristics. A further confirmation of the value of CDAI in relation to CV risk markers is the recent study by Provan, *et al*[23]. Another possible explanation for the difference in association between RA disease activity measures and CP characteristics is the relatively low number of patients, resulting in power limitations.

There were no associations between CRP and ESR and the GSM, plaque area, or numbers of CP, as shown in Figure 2 and Appendix 2. CRP/ESR reflects the inflammation status at the moment of blood sampling and is influenced by genetic variation, disease activity, and treatment. Thus, the association between CRP/ESR and plaque vulnerability might be confounded by treatment. The pathophysiology of

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Table 2. Characteristics of patients with rheumatoid arthritis according to disease activity measures.

	CDAI				SDAI				DAS28			
	Remission ≤ 2.8	LDA > 2.8 and ≤ 10	MDA + HDA > 10	MDA + HDA vs Remission p	Remission ≤ 3.3	LDA > 3.3 and ≤ 11	MDA + HDA > 11	MDA + HDA vs Remission p	Remission < 2.6	LDA ≥ 2.6 and ≤ 3.2	MDA + HDA > 3.2	MDA + HDA vs Remission p
No. patients	43	71	31		43	68	34		78	27	40	
Age, yrs, median (IQR)	64.1 (55.7–72.6)	63.5 (54.0–70.9)	60.0 (51.0–65.7)	0.07	61.7 (53.6–69.2)	63.5 (54.0–70.9)	60.4 (51.7–68.6)	0.53	62.4 (53.2–70.4)	63.5 (54.4–69.8)	61.7 (53.6–72.2)	0.91
Sex, female/male	30/13 (69.8/30.2)	55/17 (76.4/23.6)	25/6 (80.6/19.4)	0.29	31/11 (73.8/26.2)	50/18 (73.5/25.5)	29/6 (82.9/17.1)	0.34	55/23 (70.5/29.5)	23/5 (82.1/17.9)	32/8 (80.0/20.0)	0.27
Cardiovascular risk factors												
Smoking ever-never	27 (62.8)	50 (69.4)	18 (58.1)	0.81	25 (59.5)	48 (70.6)	21 (60.0)	0.84	54 (69.2)	17 (60.7)	24 (60.0)	0.41
Systolic BP, mm Hg	131.3 ± 20.2	136.3 ±21.3	133.7 ± 18.4	0.60	130.9 ± 20.5	134.9 ± 19.8	137.1 ± 21.5	0.20	132.1 ± 20.3	135.8 ± 18.3	137.5 ± 21.8	0.19
Diastolic BP, mm Hg	79.1 ± 10.0	80.7 ± 9.6	81.1 ± 9.3	0.38	79.1 ± 9.7	80.2 ± 10.1	81.9 ± 8.6	0.18	79.2 ± 10.2	82.0 ± 9.3	81.4 ± 8.5	0.22
Diabetes	1 (2.3)	8 (11.1)	4 (12.9)	0.08	1 (2.4)	7 (10.3)	5 (14.3)	0.06	6 (7.7)	1 (3.6)	6 (15.0)	0.22
Body mass index, kg/m^2	25.2 ± 3.7	26.0 ± 5.5	26.3 ± 4.9	0.27	25.6 ± 4.2	26.1 ± 5.4	25.7 ± 4.8	0.92	25.7 ± 4.4	26.2 ± 6.0	26.0 ± 5.0	0.74
Familial CVD	6 (14.0)	8 (11.1)	4 (12.9)	0.98	5 (11.9)	9 (13.2)	4 (11.4)	0.99	10 (12.8)	3 (10.7)	5 (12.5)	0.94
CVD measures												
CVD	3 (7.0)	12 (16.7)	6 (19.4)	0.10	3 (7.1)	11 (16.2)	7 (20.0)	0.09	10 (12.8)	2 (7.1)	9 (22.5)	0.16
Intima-media thickness, mm	0.76 ± 0.16	0.79 ± 0.20	0.74 ± 0.18	0.65	0.77 ± 0.16	0.78 ± 0.20	0.76 ± 0.19	0.92	0.77 ± 0.17	0.76 ± 0.17	0.78 ± 0.22	0.80
Patients with carotid plaques	23 (53.5)	49 (68.1)	14 (45.2)	0.48	22 (52.4)	45 (66.2)	18 (51.4)	0.93	48 (61.5)	15 (53.6)	23 (57.5)	0.67
No. carotid plaques	1.95 ± 0.98	2.08 ± 0.98	2.00 ± 1.11	0.90	1.86 ± 1.04	2.04 ± 0.93	2.17 ± 1.10	0.38	1.85 ± 0.90	2.07 ± 1.03	2.39 ± 1.08	0.37
No. GSM plaques	1.94 ± 1.03	1.92 ± 0.95	1.83 ± 0.94	0.78	2.00 ± 1.13	1.82 ± 0.80	1.94 ± 1.12	0.88	1.85 ± 0.91	1.73 ± 0.90	2.09 ± 1.06	0.37
Lipids												
Total cholesterol	6.1 ± 1.3	5.7 ± 1.2	5.2 ± 1.1	0.001	6.1 ± 1.2	5.7 ± 1.3	5.3 ± 1.1	0.006	5.8 ± 1.4	5.79 ± 1.1	5.47 ± 1.1	0.22
HDL cholesterol	1.8 ± 0.6	1.8 ± 0.6	1.7 ± 0.6	0.38	1.8 ± 0.6	1.8 ± 0.6	1.7 ± 0.5	0.49	1.8 ± 0.7	1.8 ± 0.6	1.7 ± 0.5	0.26
Triglycerides, median (IQR)	1.1 (0.8–1.5)	1.1 (0.8–1.5)	1.1 (0.8–1.7)	0.66	1.1 (0.8–1.5)	1.1 (0.8–1.5)	1.1 (0.8–1.6)	0.82	1.1 (0.7–1.5)	1.1 (0.9 –1.5)	1.1 (0.7–1.6)	0.69
LDL cholesterol	3.7 ± 1.0	3.3 ± 1.0	2.9 ± 1.0	0.001	3.7 ± 1.1	3.3 ± 1.0	3.0 ± 1.1	0.005	3.4 ± 1.1	3.4 ± 1.0	3.2 ± 1.0	0.39
Inflammatory markers												
ESR, mm/h, median (IQR)	11.0 (6.0–18.0)	13.0 (8.0–26.5)	13.0 (5.0–26.0)	0.40	10.0 (6.8–17.0)	13.0 (8.0–25.8)	17.0 (6.3–29.0)	0.03	9.0 (6.0–14.0)	14.0 (8.0–19.5)	26.0 (13.5–34.0)	< 0.001
CRP, mg/dl, median (IQR)	2.0 (1.0–4.0)	4.0 (2.0–9.0)	4.0 (2.0–11.0)	0.003	2.0 (1.0–3.3)	4.0 (2.0–8.0)	7.0 (3.0–21.0)	< 0.0001	3.0 (1.0–4.0)	3.0 (1.0–8.0)	7.5 (3.3–19.0)	< 0.001

Demographic data are presented as crude data, compared using Student 2-sample T-test, Mann-Whitney U test, and chi-square test as appropriate. Skewed variables were log-transformed. Median values are given as mean ± SD, numbers (%), skewed data as median with interquartile range (IQR). CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index; DAS28: Disease Activity Score based on 28-joint counts; LDA: low disease activity; MDA: moderate disease activity; HDA: high disease activity; BP: blood pressure; CVD: cardiovascular disease; GSM: Gray-Scale Median (lipids are mmol/l); HDL: high-density lipoprotein; LDL: low-density lipoprotein; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

plaque vulnerability is complex and not easy to unravel in detail with the procedure used in our project.

Even though the difference in GSM between active disease and remission was statistically significant, as measured by CDAI, it remains to be confirmed whether this finding is clinically important. Previous analyses of GSM relating to vulnerability and clinical outcomes such as stroke, death, and transient ischemic attack after carotid intervention demonstrated a GSM threshold value ≤ 25[31]. In that study, patients (not with RA) had a carotid stenosis > 70%. Although the authors found no correlation between degree of stenosis (size of plaque) and GSM, there was a significant relationship between lower GSM and clinical events after carotid artery intervention. Our patients with asymptomatic CP had much smaller CP area and were comparable to the RA patients reported by Stamatelopoulos, *et al*[32], although the GSM values were lower in the Stamatelopoulos cohort compared to ours. Possible explanations for the differences in GSM between our study and the Stamatelopoulos study are the differences in clinical charac-

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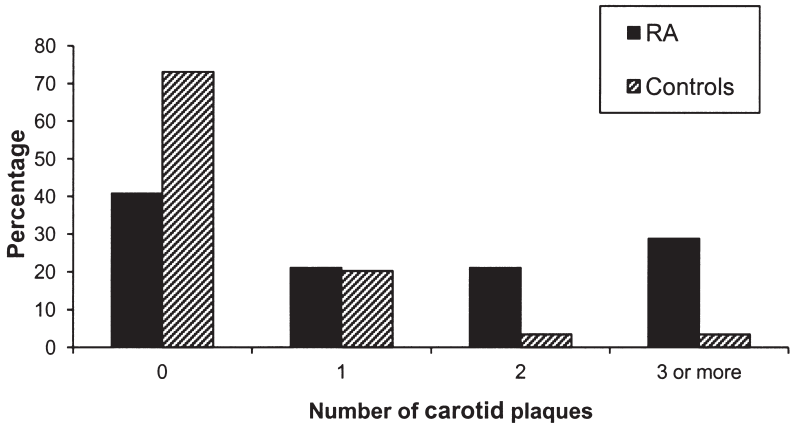

Figure 1. Number of carotid plaques in patients with rheumatoid arthritis (RA) and non-RA controls; carotid plaques shown as percentage of total number of patients and controls. Difference between groups: Poisson regression adjusted for age and sex, $p < 0.001$.

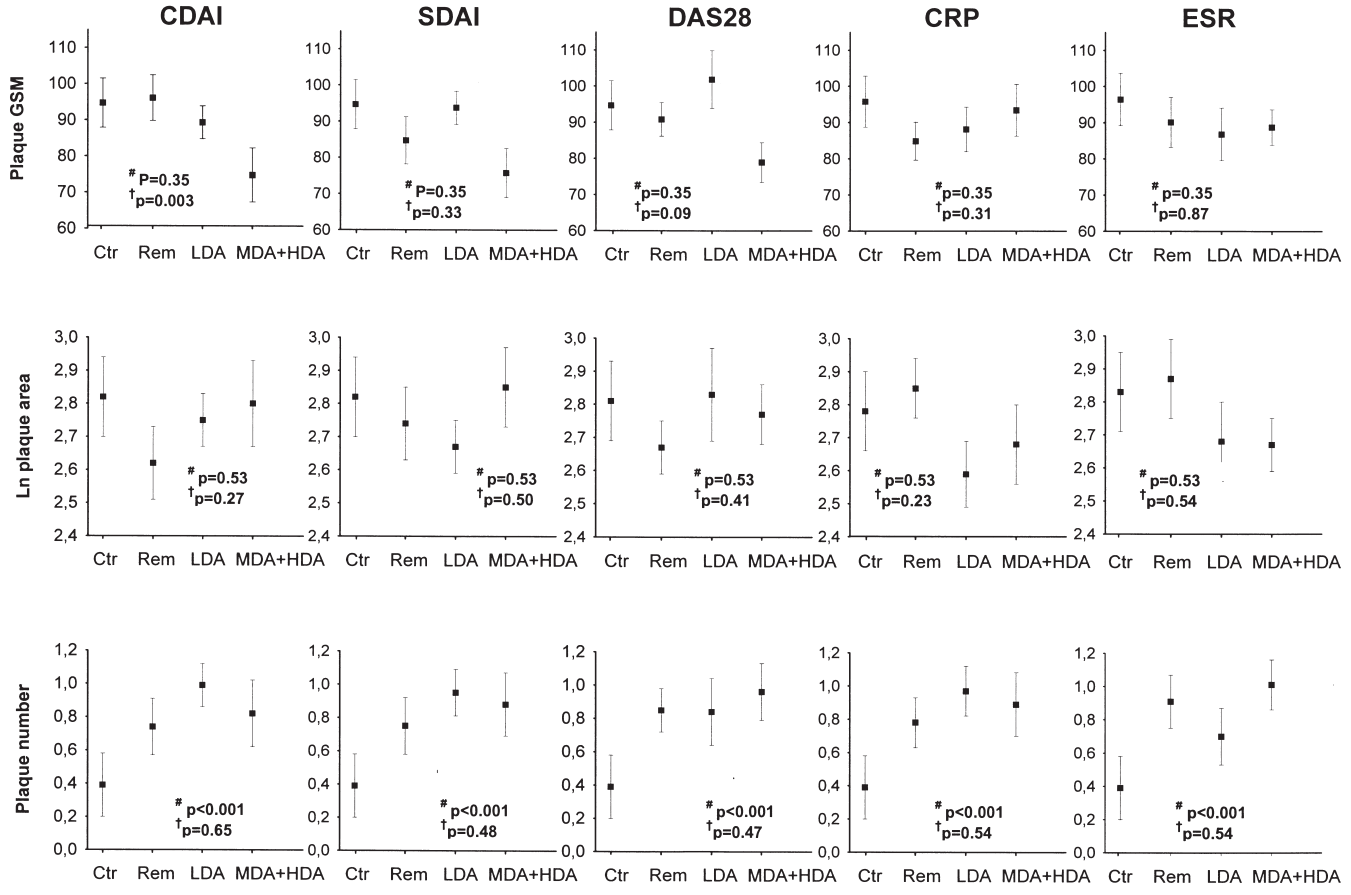

Figure 2. Characteristics of carotid artery plaque according to disease activity in patients with rheumatoid arthritis (RA) and controls. Different methods were used to compare patients and controls and trend within RA disease activity: mixed models with random intercepts were used to analyze plaque area and GSM; Poisson regression analysis was used to compare number of plaques between patients and controls. All data were adjusted for age, sex, smoking, and systolic blood pressure and are presented as least-square means with standard error. Trend analyses were performed by linear contrasts within each model. #RA vs controls; †trend in RA disease activity. CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index; DAS28: Disease Activity Score based on 28-joint counts; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Ctr: controls; Rem: remission; LDA: low disease activity; MDA: moderate disease activity; HDA: high disease activity; GSM: Gray-Scale Median.

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teristics, for example disease duration/severity, RF/ACPA status, and/or GSM image calibration methods, between the 2 cohorts.

In the general population, it has been documented that coronary plaque composition changes to more stable plaques and that plaque volume may regress, upon intensive statin therapy[33]. There is only preliminary documentation on the beneficial effect of statins on CP morphology (size and composition)[29], and no such data are available on the effect of statins on CP in patients with RA. The use of tumor necrosis factor-α (TNF-α) inhibitors has been shown to reduce the risk for CV disease in patients with RA[34,35], but data on the effect of TNF-α inhibitors on CP are not available. The analyses on the associations of statins and TNF-α inhibitors with GSM and area of CP in our study were unfortunately inconclusive because of the low number of patients. A trial on the effect of statins on CP in RA is being conducted and is expected to be reported in 2013 (clinincaltrials.gov: NCT01389388).

The increased extent of atherosclerosis with numerically more CP was associated with the presence of RA, but not with the level of RA disease activity. The RA disease activity indices reflect a short time period, in contrast to the longer time it takes to develop atherosclerotic plaques. In addition, RA has inflammatory components similar to atherosclerosis[36,37]. The association between RA and increased level of atherosclerosis and a higher number of CP therefore seems plausible. The clinical importance of the increased numbers of CP was pointed out by Evans, *et al*, who showed that when CP was present bilaterally, the risk for suffering an acute myocardial syndrome quadrupled[19]. In our cohort bilateral CP was more common in patients with RA compared to controls, which is expected because patients with RA have numerically more CP. Although the clinical importance of the localization of CP in the carotid artery is unknown, we have shown, along with others[17], that RA was associated with a high prevalence of CP in the carotid bulb-ICA region compared to the CCA region. In our cohort there were no differences between the GSM at the various locations (ICA-carotid bulb and CCA) in patients with RA and controls.

Dessein, *et al* have reported that the presence of CP in patients with RA is related to RA disease duration, age, sex, and CV risk factors such as smoking and blood pressure[30]. Surprisingly, the presence of CP in our cohort was not related to RA disease duration, but to having the disease. The discrepancy in these findings may be explained by the long disease duration in all our patients (13–20 years), whereas Dessein, *et al* had a wider span of disease duration in their report.

Hypothetically, patients with high RA disease activity could have a cluster of traditional CV risk factors. Dessein, *et al* showed that an increasing number of CV risk factors in patients with RA significantly increased the risk of having a CP[30]. By contrast, no such association between traditional CV risk factors, except for lipids, and RA disease activity was found in our patients. CV biomarkers such as lipids and both central and peripheral biomarkers (by pulse-wave velocity and augmentation index, and reactive hyperemic index, respectively) have been reported to be associated with RA disease activity[23]. Atherogenic lipid levels had an inverse relationship with increasing disease activity in our study. This observation was robust as it was present for all 3 disease activity measures (Table 2). Further, Peters, *et al* have shown that increasing CRP was associated with declining atherogenic lipid levels[38].

An important clinical question is whether it is possible to identify those patients who are at high risk of a CV event by noninvasive imaging of CP. Our results on plaque characteristics offer no conclusion regarding this important issue, because of the cross-sectional study design. The role of noninvasive vascular imaging in risk prediction of future CV events in RA remains unclear. For the time being, it is advisable to treat all RA patients with CP as high-risk patients with secondary prevention treatment targets, as recommended in the newly updated guidelines for patients with dyslipidemias[39].

There are several limitations and strengths to this study. First, the imaging modality used, B-mode ultrasound, cannot distinguish between different components of the atherosclerotic plaque as well as other imaging modalities, such as high-resolution magnetic resonance imaging (HR-MRI), which is superior to other noninvasive modalities. Especially in large arteries such as the carotids, HR-MRI gives the best information about plaque size, composition, and morphology[40]. An advantage of B-mode ultrasound is its availability and low cost compared to HR-MRI. However, the ultrasound modality is more operator-dependent with regard to performance and interpretation, compared to HR-MRI. To minimize this, all the carotid ultrasound examinations in our study were performed by 1 experienced sonographer together with a senior cardiologist (AGS). A further limitation is that our study was small, and therefore has limited power and must be interpreted to be of a hypothesis-generating character. Plaque size and area is a complex matter concerning CV events. An ultrasound area measurement of a CP is a 2-dimensional (2-D) analysis and hence has greater possibilities for measurement errors of size than, for example, 3-D methods. Thus a 2-D method for characterizing plaque area may not accurately represent the state of atherosclerosis. This is a limitation of our study. It is well known that CV events occur on smaller atherosclerotic plaques. For instance, Falk, *et al*[41] showed that most myocardial infarctions arise from small stenoses with < 50% occlusion of the coronary artery. We are not aware of any similar study on carotid artery plaque area. Taking all this into consideration, we chose to add carotid plaque area to our analysis. In

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APPENDIX 1. Number of carotid artery plaques in controls and patients with rheumatoid arthritis (RA) at different disease activity levels. Poisson regression was used for analyzing the number of plaques per patient, comparing patients with RA and controls and trend within RA disease activity. Values are adjusted for age, sex, smoking, and systolic blood pressure, and presented as least-square means with standard error. Trend analyses were performed by linear contrasts within each model.

Controls	Patients with RA					
	Measure	Remission	LDA	MDA + HDA	p, RA vs Controls	Trend in RA Disease Activity
0.39 (0.19)	CDAI	0.74 (0.17)	0.99 (0.13)	0.82 (0.20)	< 0.0001	0.65
0.38 (0.19)	SDAI	0.75 (0.17)	0.95 (0.14)	0.88 (0.19)	< 0.0001	0.48
0.38 (0.19)	DAS28	0.85 (0.13)	0.84 (0.20)	0.96 (0.17)	< 0.0001	0.47
0.38 (0.19)	CRP	0.78 (0.15)	0.97 (0.15)	0.89 (0.19)	< 0.0001	0.54
0.38 (0.19)	ESR	0.91 (0.16)	0.70 (0.17)	1.01 (0.15)	< 0.0001	0.54

CDAI: Clinical Disease Activity Index, SDAI: Simplified Disease Activity Index; DAS28: Disease Activity Score based on 28-joint counts; LDA: low disease activity; MDA: moderate disease activity; HDA: high disease activity; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

APPENDIX 2. Carotid artery plaque characteristics in controls and in patients with rheumatoid arthritis (RA) at different disease activity levels. For CRP, remission, LDA, MDA + HDA classes were set to 0–3, 4–10, and > 10 mg/dl, respectively. For ESR, remission, LDA, MDA + HDA classes were set to 1–8, 9–15, and > 15, respectively. GSM: Gray-Scale Median; minimum GSM: the lowest GSM of a plaque in a person; In area: the natural logarithm of the plaque area. Different methods were used to compare patients and controls and trend within RA disease activity: mixed models with random intercepts were used to analyze plaque area and GSM, and an analysis of covariance model was used for comparative analyses of minimum GSM. All data were adjusted for age, sex, smoking, and systolic blood pressure and are presented as least-square means with standard error. Various groups were created (controls, remission, LDA, MDA + HDA) in mixed models. Because of differences in the disease activity indexing, the estimate for the control group differs slightly. This does not reflect disease activity in the control group. Trend analyses were performed by linear contrasts within each model.

	Controls	Patients with RA					
		Measure	Remission	LDA	MDA + HDA	p, RA vs Controls	Trend in RA Disease Activity
GSM	94.69 (6.80)	CDAI	96.09 (6.31)	89.33 (4.52)	74.78 (7.44)		0.03
	94.35 (6.71)	SDAI	84.71 (6.51)	93.74 (4.59)	75.78 (6.77)	0.35	0.33
	94.96 (6.72)	DAS28	90.84 (4.65)	101.82 (7.96)	78.91 (5.48)		0.09
	95.78 (7.05)	CRP	84.89 (5.25)	88.13 (6.14)	93.40 (7.14)		0.31
	96.41 (7.18)	ESR	90.12 (6.96)	86.80 (7.26)	88.72 (4.89)		0.87
Minimum	88.38 (6.64)	CDAI	89.50 (7.09)	78.55 (5.11)	65.99 (8.17)		0.03
GSM	88.01 (6.64)	SDAI	78.18 (7.34)	84.07 (5.27)	66.13 (7.48)	0.23	0.24
	88.11 (6.58)	DAS28	81.31 (5.23)	94.23 (8.73)	68.65 (6.22)		0.11
	89.33 (7.03)	CRP	74.50 (6.05)	82.94 (6.55)	79.13 (8.38)		0.63
	89.33 (7.09)	ESR	81.63 (7.32)	79.64 (7.99)	77.18 (5.71)		0.63
In area	2.82 (0.12)	CDAI	2.62 (0.11)	2.75 (0.08)	2.80 (0.13)		0.27
	2.82 (0.12)	SDAI	2.74 (0.11)	2.67 (0.08)	2.85 (0.12)	0.53	0.50
	2.81 (0.12)	DAS28	2.67 (0.08)	2.83 (0.14)	2.77 (0.09)		0.41
	2.78 (0.12)	CRP	2.85 (0.09)	2.59 (0.10)	2.68 (0.12)		0.23
	2.83 (0.12)	ESR	2.87 (0.12)	2.68 (0.12)	2.67 (0.08)		0.54

CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index; DAS28: Disease Activity Score based on 28-joint counts; LDA: low disease activity; MDA: moderate disease activity; HDA: high disease activity; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

addition, the response rate of controls invited to participate in the study was 43.5%, whereas 57% of surviving members of the EURIDISS and ORAR registries agreed to participate at the 15- and 10-year followup, respectively. Such loss of followup regularly occurs in longitudinal studies, but may be a source of potential selection bias. It is also possible that a selection bias may have occurred because of the higher level of nonparticipation in the controls. Confirmation of our results is warranted in larger studies. In addition, longitudinal data are needed to determine whether the various CP characteristics make any clinical difference concerning CV outcome measures.

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We conclude that patients with active RA disease assessed by CDAI seem to have more vulnerable CP compared to those in remission, pointing to the importance of achieving RA remission goals to reach a state of stable atherosclerotic disease. The increased extent of atherosclerosis with numerically more CP was associated with the presence of RA and, surprisingly, not with RA disease activity.

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