Published in final edited form as:

Arthritis Rheum. 2011 May ; 63(5): 1211–1220. doi:10.1002/art.30265.

CAROTID ATHEROSCLEROSIS PREDICTS INCIDENT ACUTE CORONARY SYNDROMES IN RHEUMATOID ARTHRITIS

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Abstract

Objective—The role of atherosclerosis in the acute coronary syndromes (ACS) that occur in patients with rheumatoid arthritis (RA) has not been quantified in detail. We determined the extent to which ACS are associated with carotid atherosclerosis in RA.

Methods—We prospectively ascertained ACS, defined as myocardial infarction, unstable angina, cardiac arrest or death due to ischemic heart disease in an RA cohort. We measured carotid atherosclerosis using high-resolution ultrasound. We used Cox proportional hazards models to estimate the association between ACS and atherosclerosis, adjusting for demographics, CV risk factors, and RA manifestations.

Results—We performed carotid ultrasound on 636 patients, whom we followed 3,402 person-years. During this time, 84 patients experienced 121 new or recurrent ACS, a rate of 3.5 ACS per 100 patient-years (95% CI 3.0, 4.3). Among the 599 patients without prior history of ACS, 66 incident ACS occurred over 3,085 person-years, an incidence of 2.1 ACS per 100 person-years (95% CI 1.7, 2.7). The incidence of new ACS per 100 patient-years among patients without plaque was 1.1 (0.6, 1.7); with unilateral plaque 2.5 (1.7, 3.8); and with bilateral plaque 4.3 (2.9, 6.3). Covariates associated with incident ACS independent of atherosclerosis included male sex, diabetes mellitus, and a cumulative glucocorticoid dose of ≥ 20 grams. In addition, hypertension and the number of swollen joints were associated with new or recurrent ACS.

Conclusions—Atherosclerosis is strongly associated with ACS in RA. Patients with carotid plaque, multiple CV risk factors, particularly diabetes or hypertension, many swollen joints, high cumulative dose of glucocorticoids or who are men, are at high risk of ACS.

Indexing terms

Rheumatoid Arthritis; Cardiovascular Risk Factors; Atherosclerosis; Systemic Inflammation; Carotid Intima-media Thickness

INTRODUCTION

Rheumatoid arthritis (RA) is associated with an increased susceptibility to cardiovascular (CV) disease, and related mortality.^{1–5} The physiopathology of the increased CV risk is not fully understood at this time. Known CV risk factors and systemic inflammation increase the CV propensity, as they do in people without RA.^{6–9} These are thought to contribute to atherosclerosis,¹⁰ which in the general population is a strong predictor of CV disease. However, there have been few efforts to quantify the role of atherosclerosis as a determinant of CV morbidity in RA.¹¹ The objective of the current analysis was to estimate the contribution of atherosclerosis to acute coronary syndromes (ACS) in RA.

SUBJECTS AND METHODS

Patients

From 1996 through 2001, we enrolled 779 consecutive patients with RA defined according to established criteria,¹² into a prospective study, known ÓRALE for Outcome of Rheumatoid Arthritis Longitudinal Evaluation. After a baseline evaluation at the recruitment site, we invited patients for annual follow-up assessments at a clinical research center. Between February 2000 and February 2003, we invited all patients for an additional visit to perform a high-resolution B-mode carotid ultrasound.

CV risk factor assessment

We recorded the CV risk factors at the baseline evaluation, and at each annual follow-up visit up. Medical records were reviewed thoroughly. We considered hypertension present if the diagnosis was recorded by a physician, if patients received antihypertensive medications, or if the systolic/diastolic blood pressure measured by us was $\geq 140 / \geq 90$ mmHg. For obesity, we measured height and weight at each visit and calculated the body mass index (BMI, kg/M^2). Patients were considered obese if BMI was ≥ 30 . We considered diabetes mellitus and hypercholesterolemia present if either diagnosis was recorded by a physician in a medical record, or if anti-diabetic or lipid-lowering drugs were prescribed. In addition, we considered patients to have hypercholesterolemia if their fasting plasma cholesterol measured by us during a study visit was ever 200 mg/dl or higher, and diabetes if the fasting blood sugar was ≥ 126 mg/dL. We classified patients as current smokers if they continued to smoke at the time of the initial study visit, and former smokers if they had quit before that time.

Musculoskeletal examination

At each visit, we assessed 28 joints for tenderness or pain on motion and swelling, and 48 joints for deformity.¹³ We also assessed patients for the presence or absence of subcutaneous nodules using a standardized protocol.

Assessment of disease activity

In addition to tenderness and swelling in 28 joints, we measured the Westergren erythrocyte sedimentation rate (ESR) at each visit. We used these three variables to calculate the 28-joint Disease Activity Index (DAS28).¹⁴

Ascertainment of glucocorticoid use

We assessed glucocorticoid exposure as described previously.¹⁵ Briefly, at each visit patients were asked whether they were receiving glucocorticoids and, if so, were asked for the date they were first prescribed and the dose. We verified this information with their list of medications and by pharmacy and medical records. We estimated the cumulative oral

glucocorticoid dosage by multiplying the current daily dose by the number of days since glucocorticoids were initiated. For alternate day or on other non-daily schedules, we averaged the dose to obtain the daily amount. We considered patients who received intrarticular, intramuscular or oral glucocorticoids less often than monthly as not having received glucocorticoids. At each follow-up visit, we updated information on glucocorticoid use and dosage, and if still using, we calculated the cumulative dose since the previous visit. We did not consider dose changes between study visits. The total cumulative glucocorticoid dose is provided by the summed dose over each interval, expressed in prednisone equivalents. We stratified the cumulative glucocorticoid dose into various quantiles, to determine if there was a threshold above which ACS increased significantly.

Carotid Ultrasound

One technician performed a duplex scan of the carotid arteries in all patients, following a standardized vascular protocol developed for the Multi-Ethnic Study of Atherosclerosis.¹⁶ We used an ATL HDI-3000 High Resolution Imaging machine with a L7-4 Transducer (Philips Medical Systems North America Company, Bothell, WA). The technician acquired 4 standardized B-mode images and a Doppler flow measurement from both sides of the neck. The first image was of the distal common carotid artery, and the three others were centered on the site of maximum near and far wall thickening in the proximal internal carotid artery or carotid bulb. Results were recorded on Super VHS tape and mailed to a central facility (Ultrasound Reading Center, New England Medical Center, Boston, MA), for grading of the carotid artery intima-media thickness (IMT) and carotid plaque. At the reading center, the images were digitized at 30 frames per second, and arterial diameter fluctuations with the cardiac cycle observed. Images were selected and read by a single, certified reader masked to subject characteristics. Carotid plaque was identified as a discrete projection of 50% or more from the adjacent wall into the vessel lumen. For the IMT, we measured in end diastole at each of the near and far walls of the right and left common carotid arteries, and the anterior oblique, lateral and posterior oblique views of the internal carotid artery, for a total of 16 IMT measurements per person. The maximal IMT of the common and internal carotid arteries were obtained by averaging the maximal measurement from the near and far walls at each projection, from the right and left sides. Then the composite maximal IMT was calculated by averaging the common and internal carotid maximal IMT values. The result is one IMT value per person, expressed in millimeters. Our study involved a single ultrasonographer and a single reader. Nevertheless, to assess the technique's reliability, our reader re-read 50 images, and a different reader re-read a separate set of 50 images. The intra-reader intraclass correlation coefficient for CaIMT was 0.99, and the inter-reader coefficient was 0.94. For plaque, the intra-reader kappa statistic was 1.0, while the inter-reader kappa was 0.94.

Acute Coronary Syndromes

ACS were defined as unstable angina, myocardial infarction, cardiac arrest, or death with ischemic heart disease listed as the first or first underlying cause of death in the death certificate. At baseline and at each follow-up examination, a physician interviewed all patients about the occurrence of hospitalizations and comorbidity, with specific attention to ACS and other CV events, including coronary revascularization procedures. Patients provided a written release of medical records as part of the study protocol, and thus, complete records of all reported events were obtained and reviewed. Past events were ascertained initially at the baseline evaluation. Information on new ACS was updated at subsequent study visits. Area hospitals were contacted annually to determine if cohort members were hospitalized, in which case, full medical records were obtained. All ACS events were ascertained with dates and confirmed by medical records. Deaths were identified from a variety of sources including next-of-kin, physicians, obituaries and local

health departments. Online mortality databases were searched monthly using *ad hoc* computer programs. All deaths were confirmed by death certificate. Events were systematically adjudicated using standardized criteria by a board certified cardiologist,^{17,18} who was provided with results of invasive and non-invasive tests pertaining to the event, but was masked to other clinical characteristics, including the results of the carotid ultrasound. Events were considered incident if the patient had not experienced any previous ACS.

Statistical analysis

We compared patients' characteristics at the time of enrollment into ÓRALE, according to the presence or absence of a history of ACS, using t-tests or chi-square as indicated. We used a time-to-event approach to estimate the association between the carotid ultrasound findings (IMT or plaque) and the occurrence of ACS. All patients contributed observation time from the time of enrollment until their last study visit, or the censoring date of December 31, 2004. We performed two analyses, in both of which observation time began on the date of enrollment into the ÓRALE study. In the first analysis, we studied the incidence of new ACS occurring during observation in patients who had never experienced a CV event prior to enrollment in ÓRALE. In the second analysis we considered both new and recurrent events occurring during observation. In the latter of these analyses, we considered events that occurred before enrollment as past events, using an indicator variable. We did not consider non-fatal ACS that occurred after the date of last visit or after the censoring date. We plotted the survival function of patients grouped according to the presence of carotid plaque, using the Kaplan-Meier product limit technique.¹⁹ Our interest was to estimate the association between carotid IMT or plaque and ACS. We used Cox proportional hazards modeling to adjust for potential confounders, which were entered as covariates in multivariable models. The values for sex, race, smoking history and the carotid ultrasound were fixed and did not vary over the observation period. All other variables were available as time varying-covariates. We considered covariates in two ways in separate models: as the non-varying values obtained at the initial examination, and as time-varying covariates.²⁰ We also tested models that included quadratic terms for age and body mass index. We used a step-wise selection approach to multivariable model building, beginning with a full model, removing variables if their association with ACS had $P \geq 0.075$ and re-entering them if $P \leq 0.05$. We used robust variance estimates in the recurrent-event models, adjusted for within-person clustering. We report 95% for all estimates. All analyses were done using the Stata/SE 8.2 software package (StataCorp LP, College Station, Texas).

RESULTS

We have described the characteristics of the 779 ÓRALE cohort members in previous publications.^{10, 21} When we began the carotid ultrasounds, in February 2000, 66 patients had died and 32 moved away from San Antonio. This left 681 patients still eligible for ultrasound scanning. Of these, we could not establish contact with 12, 19 declined participation, and in 13, we did not obtain an ultrasound scan because our evaluation was done at their residence. We thus performed a high resolution carotid ultrasound on 637 patients (93.5% of eligible). In one subject, the image was not of sufficient quality for an IMT measurement, and that patient was omitted from analysis, leaving 636 patients with data for analyses. Table 1 shows the clinical characteristics of the patients, according to whether or not they had experienced incident or recurrent CV events.

By the censoring date of December 31, 2004, the 636 patients who had a carotid ultrasound had accrued 3,402 person-years of observation. During this time, 84 of the patients experienced 121 ACS events, a rate of 3.5 per 100 person years, 95% CI 2.8, 4.6. Of these, 71 were non-fatal myocardial infarctions, 24 were episodes of unstable angina, 13 were fatal ischemic heart disease, 10 were fatal myocardial infarctions, and 3 fatal cardiac arrests.

The 599 patients who had no prior history of ACS accrued 3,085 person-years of observation, during which there were 66 incident ACS events, for an incidence rate of 2.1 ACS per 100 person-years, 95% CI 1.7, 2.7. Of these 41 were non-fatal myocardial infarctions, 9 were unstable angina, 8 were fatal ischemic heart disease, 5 were fatal myocardial infarctions, and 2 were fatal cardiac arrests.

Table 2 shows the number of events, observation period and rate of ACS over time, according to the extent of carotid plaque. We classified patients as having unilateral, bilateral or no plaque. The rate of events was higher in patients with more extensive plaque in a “dose-dependent” pattern: Compared to patients who were plaque-free, the rate of ACS among patients with unilateral plaque more than doubled, and among patients with bilateral plaque, the rate nearly quadrupled. The differences between patients with no plaque, unilateral and bilateral plaque were statistically significant. This pattern was accentuated when both new and recurrent events were considered together (Table 2).

Figure 1 shows Kaplan-Meier curves illustrating the probability of incident ACS and all ACS during the period of observation. Both graphs suggest a progressively higher risk of ACS depending of the extent of carotid plaque. In both of these graphs, the survival function was plotted without adjusting for age or sex. After adjustment for these two variables, the plots changed little. Figure 2 shows the incidence of ACS in the ÓRALE cohort and of MI in the Cardiovascular Health Study,²² according to IMT quintiles.

We performed multivariable Cox proportional hazards regression to examine the extent to which the plaque-ACS association shown in Table 2 was independent of confounders such as age, sex and other covariates. In these analyses, we noted that the association between the carotid ultrasound variables and ACS varied little when baseline or time-varying covariates were included in the models. However, the covariates that were selected differed somewhat when baseline or time-varying values for the covariates were included in the models. In Tables 3 and 4, we show the models that included baseline variables for the covariates. Table 3 shows baseline characteristics associated with the occurrence of incident ACS in patients among whom ACS had not previously occurred. For this analysis, there were a total of 66 incident ACS during observation. In the bivariate analysis, the three demographic variables were associated with incident ACS, as were diabetes mellitus and hypertension, the deformed joint count, cumulative glucocorticoids and the carotid IMT. In stepwise multivariable models that did not include a carotid ultrasound variable, the variables independently associated with incident ACS were: male sex, non-Hispanic White ethnicity, diabetes mellitus, hypertension and cumulative glucocorticoids. When we added a carotid ultrasound variable to this model, the only variables that remained significantly associated with incident ACS were male sex, diabetes mellitus, and a cumulative glucocorticoid dose of at least 20 grams (Table 3). In this model, the hazard ratio associated with the IMT was 1.31 per standard deviation difference, 95% CI 1.02, 1.70; $P \leq 0.001$. Not shown in Table 3, we re-ran this model using plaque instead of the IMT: the hazard ratio for unilateral plaque was 2.02 (1.07, 3.84) and for bilateral plaque it was 2.96 (1.55, 5.62). In interpreting these findings on incident ACS, it is important to consider that with 66 events associated with a dichotomous exposure that was present in half the patients, as was the case with plaque, the minimum detectable hazard ratio is about 1.99.²³ Thus, these results do not rule out associations that are less strong between the other covariates we studied, and incident ACS. We did not include treatment with anti-TNF agents in the model because no CV events occurred among the patients receiving these agents at baseline (Table 1), which precludes Cox modeling.

When we tested models using time-varying covariates, only male sex and hypertension were associated with incident ACS, both of which remained significant when carotid plaque or IMT were added to the model.

In Table 4 we examine the association between the same set of baseline predictors and ACS, considering both new and recurrent events. In this analysis, we did not exclude patients who had experienced CV events prior to entry into ÓRALE. Moreover, since patients who survived an ACS remained at risk of experiencing a second and subsequent events, we considered recurrent events as well, using robust standard errors to avoid type I or false-positive errors. There were 121 such ACS events for analysis. In the bivariate analyses, variables associated with ACS events were: demographics, cumulative glucocorticoid of 20 grams or more, RA duration, all of the CV risk factors except for body mass, a past history of CV events, and the carotid IMT. In the multivariable analysis that did not include past CV events or the carotid IMT, the factors associated with ACS included age at fist visit, male sex, diabetes, hypertension, the swollen joint count and cumulative glucocorticoids. Upon adding past CV events and the carotid IMT to the model, all, except for age, remained independently associated with ACS (Table 4). We re-tested this same model after substituting carotid plaque for IMT, and the hazard ratio (95% CI) for unilateral plaque was 2.54 (1.39, 4.64). For bilateral plaque the hazard ratio was 5.89 (3.22, 10.78).

We tested the above model for incident and recurrent ACS, using time-varying covariates, with results that differed somewhat from the baseline model. In the time-varying model, age, male sex, diabetes mellitus, hypertension, subcutaneous nodules and the number of swollen joints were associated with ACS. However, upon adding past CV events and the carotid IMT to the model, only nodules and swollen joints remained associated with new and recurrent ACS, suggesting that their mechanism of association with ACS is independent of atherosclerosis.

DISCUSSION

Our results suggest that atherosclerosis contributes significantly to ACS in RA. This may at first seem unsurprising, considering the effects of atherosclerosis in the general population. However, RA patients have a high rate of CV disease, a problem which remains incompletely understood. Until recently, even major monographs about RA did not mention atherosclerosis, and attributed myocardial infarction in RA patients to coronary arteritis.²⁴ While it is still possible that this and other mechanisms could operate in RA, our findings suggest atherosclerosis is a major factor in RA's CV complications.

Despite only 66 incident ACS events for analysis, carotid atherosclerosis provided a strong signal that was readily detected by our study. The presence of plaque in both internal carotid arteries nearly quadrupled the incidence of new ACS, compared to patients without carotid plaque. This was independent of all potential confounders available to us, including age, sex and the remaining variables in Table 3. This supports the notion that atherosclerosis is in the causal pathway, as a mediating variable between CV risk factors and ACS, rather than a confounder. The association between ACS and diabetes or hypertension, was weakened when ultrasound findings were added to the model (Tables 3 & 4), supporting the mediating role for atherosclerosis. That the two nevertheless remained independently associated with ACS serves to refocus attention on their importance determining the occurrence of CV events in RA.²⁵

The absence of the remaining variables from the predictive model should not be interpreted to mean that they are unassociated with ACS, but rather, that more outcome events (i.e. more statistical power) would be needed to detect their weaker signals. Alternatively, their

absence from the predictive model could mean that their association with ACS is mediated through atherosclerosis, as measured by the carotid IMT. An example of the latter is shown in Table 4, where age loses its association with ACS upon adding atherosclerosis markers to the model, suggesting that age is associated with ACS by the mechanism of atherosclerosis accrual over time.

In the analysis for multiple events, the effect of carotid atherosclerosis was even stronger than for incident events. Here, bilateral plaque raised the rate of events by a factor of almost eight. The multivariable analysis paralleled the incident event analysis in that atherosclerosis remained a strong predictor. This analysis also allowed us to estimate the effect of an alternative definition of atherosclerosis, based on the existence of CV events prior to enrollment into the ÓRALE cohort. This variable was also a strong predictor of the occurrence of ACS during observation.

Manifestations of RA and its treatment, including swollen joints, exposure to a high cumulative dose of prednisone, and in time-varying models, nodules, were significantly associated with multiple ACS. These variables were independent of atherosclerosis defined by the carotid IMT or plaque, and also the past history of CV events. This statistical independence suggests that they affect ACS occurrence through a pathway that may be biologically independent of atherosclerosis. Both swollen joints and subcutaneous nodules are inflammatory and extra-articular features of RA, respectively. Their association with ACS further propels inflammation and extra-articular disease into the spotlight of CV disease in RA.

Accumulating evidence suggests that systemic inflammation plays a role in atherogenesis, and in CV morbidity and mortality.^{26–33} In addition to the high-grade inflammation seen in rheumatoid joints, blood from RA patients also displays a high concentration of inflammation mediators such as IL-1 and of TNF α .^{34–38} These mediators up-regulate cell-mediated immunity, promoting inflammatory cell migration through the vascular endothelium, resulting in endothelial dysfunction.^{39–40} This is a common finding in many chronic inflammatory disease states,^{41–42} and has been demonstrated in patients with RA,^{43–45} including patients who are young and do not possess any classic risk factors for atherosclerosis.⁴⁶ In a previous study by our group,¹¹ RA manifestations were most strongly associated with atherosclerosis in younger patients, while in older ones, the traditional CV risk factors were more important. This suggests that systemic inflammation exerts its effects on the vasculature early in RA. In addition, increased extra-articular manifestations and high number of involved joints, poor functional status, and rheumatoid nodules have consistently been found to predict CV-related mortality in RA.^{47–50} Our findings therefore suggest that subcutaneous nodules and increased swollen joint counts likely reflect systemic inflammation, and may themselves be considered independent predictors of ACS in patients with RA.

It is of interest to consider whether the presence of atherosclerosis in RA patients is more predisposing to ACS than is the case in people without RA. Although a non-RA control group was not available to us to directly address this question, studies in the existing literature suggest that the predictive properties of the IMT is similar in both populations. In their meta-analysis of the ability of the IMT to predict CV events in the general population,⁵¹ Lorenz and colleagues report a pooled, adjusted and standardized hazard ratio for MI associated with the IMT of 1.17 (1.13, 1.22), well within the confidence interval of 1.02 to 1.70 that we found (Table 3). O’Leary and colleagues, using the same carotid ultrasound protocol that we employed here, reported the incidence of myocardial infarction according to IMT quintiles in the Cardiovascular Health Study, which sampled community dwelling adults from the general population.²² Figure 2 shows the data from O’Leary’s et al’s and

the present study, side by side. Although we caution readers not to view this graph as a formal comparison because, among other differences, the outcome variable of the two studies was not identical, it suggests that the role of atherosclerosis in explaining CV events in RA is quantitatively similar to that observed in the general population.

In addition to the limit in our power to detect weak associations caused the number of ACS events that occurred, our study is also subject to potential limitations due to event misclassification and lack of information about events that may have occurred after a patient's last visit. We were careful to avoid misclassification by confirming all self-reports with medical records, which were then adjudicated by a cardiologist. We did not consider ACS after the last patient visit, nor event-free time after that date. Extending observation time to include more events would likely increase statistical power, allowing us to detect weaker associations that did not reach significance in the present analysis.

Two conclusions are possible from the observations presented. First, that atherosclerosis, as measured by carotid ultrasound, is an important predictor of ACS in RA. This suggests that interventions to prevent or reduce atherosclerosis have the potential to decrease the incidence of ACS in RA. Carotid ultrasound also has potential as a tool to stratify CV risk in patients with RA, and maybe other rheumatic diseases. The technology is ubiquitous, non-invasive, radiation-free and reasonably priced. Moreover, the American College of Cardiology Foundation/American Heart Association has recommended ultrasound measurement of the carotid IMT as a reasonable tool for CV risk assessment in asymptomatic adults at intermediate risk.⁵²

Second, CV risk factors, RA manifestations and their treatment, are associated with ACS, independent of the extent of atherosclerosis. This may implicate inflammatory mechanisms in the genesis of ACS in RA. For a better understanding of such mechanisms, further research is needed. In the meantime, physicians who see patients with RA should be aware that those with diabetes mellitus, hypertension, high swollen joint counts, nodules, high cumulative doses of glucocorticoids and men with RA, are at high risk of acute coronary events.

Acknowledgments

This research was supported by grants K23 HL004481, RO1 HL085742, RO1 HD037151 and UL1RR025767 from the National Institutes of Health

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Figure 1.

Kaplan-Meier curves of the association between carotid plaque and ACS in patients with RA. Left: Probability of remaining free of an initial ACS event among 599 RA patients with no previous ACS. Only 66 first lifetime events considered. Right: Probability of remaining ACS event free among all 636 RA patients who had a carotid ultrasound. All 121 events that occurred during observation, new and recurrent, were considered.

Figure 2. Incidence of acute coronary syndromes in members of the ÓRALE cohort and of myocardial infarction in the Cardiovascular Health Study (CHS), according to carotid IMT, as reported by O’Leary et al.²² Error bars represent Poisson 95% confidence intervals.

Table 1

Baseline characteristics of 636 patients with rheumatoid arthritis (RA), according to occurrence of acute coronary syndromes

VARIABLE	Acute Coronary Syndrome (ACS)		
	Never [‡]	Past and/or Recurrent	Incident
Demographics			
Number of patients	533	37	66
Age, mean (SD)	53 (13)	67 (9) ***	58 (11) ***
Men, n (%)	124 (23)	23 (62) ***	29 (44) ***
White, n (%)	165 (31)	23 (62) ***	26 (39)
CV Risk Factors			
Diabetes mellitus, n (%)	62 (12)	7 (19)	17 (26) ***
Hypercholesterolemia, n (%)	32 (6)	10 (27) ***	4 (6)
Hypertension, n (%)	246 (46)	28 (76) ***	41 (62) *
Past smoker, n(%)	207 (38)	26 (70) **	26 (39)
Current smoking, n (%)	99 (19)	4 (11)	15 (23)
Body mass index, mean (SD)	29.0 (6.5)	28.2 (4.0)	29.2 (4.9)
Three or more CV risk factors, n (%)	31 (6)	11 (30) ***	14 (21) ***
RA Manifestations			
Duration, years, mean (SD)	9.5 (9.6)	15.9 (12.7) ***	11.1 (12.7)
Tender joint count, mean (SD)	14 (13)	14 (12)	16 (14)
Swollen joint count, mean (SD)	7 (7)	8 (9)	8 (8)
Deformed joint count, mean (SD)	9 (10)	11 (10)	12 (12) *
Subcutaneous nodules, n (%)	151 (28)	13 (35)	22 (33)
Rheumatoid factor, n (%)	411 (77)	27 (73)	11 (85)
ESR, mm/hour, mean (SD)	39 (25)	32 (22)	46 (28)
DAS28, mean (SD)	5.4 (1.5)	5.1 (1.5)	5.6 (1.6)
RA Treatment			
Methotrexate, n (%)	321 (60)	24 (65)	42 (64)
Hydroxychloroquine, n (%)	94 (18)	4 (11)	11 (17)
Currently on glucocorticoids, n (%)	265 (50)	23 (62)	33 (50)
Cumulative glucocorticoids dose $\geq$ 20 g, n (%)	36 (7)	6 (16) *	11 (17) **
Anti-TNF- α agents, n (%)	17 (3)	0 (00)	0 (00)
Carotid Ultrasound			
Carotid IMT, mean (SD)	1.090 (0.552)	1.707 (0.678) ***	1.393 (0.636) ***

VARIABLE	Acute Coronary Syndrome (ACS)		
	Never [‡]	Past and/or Recurrent	Incident
Carotid plaque			
Unilateral, n (%)	146 (27)	12 (32)**	22 (33)***
Bilateral, n (%)	102 (19)	21 (57)**	27 (41)***

ACS denoted any acute coronary syndrome occurring during patient's lifetime, before and/or after entry into study.

[‡]Referent group

CV = Cardiovascular; IMT = Intima-media thickness; ESR = erythrocyte sedimentation rate

* $P \leq 0.05$;

** $P \leq 0.01$;

*** $P \leq 0.001$

Table 2

Rate of incident and all acute coronary syndromes in patients with rheumatoid arthritis, according to the extent of carotid plaque on ultrasound.

Plaque	Incident Acute Coronary Syndromes (n = 599)			All Acute Coronary Syndromes (n = 636)		
	Events	Person-Years	Rate* (95% CI)	Events	Person-Years	Rate* (95% CI)
None	17	1,581	1.1 (0.6, 1.7)	19	1,633	1.2 (0.7, 1.8)
Unilateral	22	877	2.5 (1.7, 3.8)	36	970	3.7 (2.7, 5.1)
Bilateral	27	628	4.3 (2.9, 6.3)	66	799	8.3 (6.5, 10.5)

* Rate per 100 person years

Table 3

Bivariate and stepwise multivariable analyses of baseline factors associated with incident acute coronary syndromes in 599 patients with RA who underwent carotid ultrasound.[‡]

VARIABLE	Bivariate	SW Multivariable	
		Without IMT	With IMT
Demographics			
Age at first visit (per 10 years)	1.50 (1.22, 1.85)***	-	-
Men vs. Women	2.24 (1.38, 3.65)***	2.33 (1.39, 3.87)***	1.84 (1.07 3.15)*
White vs. non-White	1.93 (1.72, 3.20)**	1.80 (1.05, 3.06)*	1.59 (0.93, 2.73)
CV Risk Factors			
Diabetes mellitus (0, 1)	3.60 (1.36, 4.09)**	2.59 (1.44, 4.65)***	2.49 (1.38, 4.48)**
Hypercholesterolemia (0, 1)	1.12 (0.41, 3.08)	-	-
Hypertension (0, 1)	2.01 (1.23, 3.32)**	1.91 (1.14, 3.19)*	1.66 (0.98, 2.81)
Past smoking (0, 1)	1.19 (0.69, 2.07)	-	-
Current smoking (0, 1)	1.22 (0.65, 2.33)	-	-
Body mass index (Kg/M ²)	1.00 (0.96, 1.03)	-	-
RA Manifestations			
RA duration (per year)	1.02 (0.99, 1.04)	-	-
Tender joint count (per joint)	1.01 (0.99, 1.03)	-	-
Swollen joint count (per joint)	1.01 (0.98, 1.05)	-	-
Deformed joint count (per joint)	1.02 (1.01, 1.04)*	-	-
Subcutaneous nodules (0, 1)	1.01 (0.60, 1.67)	-	-
Rheumatoid factor (0, 1)	1.42 (0.72, 2.79)	-	-
ESR (per 10 mm/hour)	1.09 (0.99, 1.19)	1.08 (0.99, 1.19)	-
DAS28 (per unit)	1.06 (0.94, 1.20)	-	-
RA Treatment			
Methotrexate (0, 1)	0.96 (0.59, 1.57)	-	-
Hydroxychloroquine (0,1)	0.94 (0.41, 2.11)	-	-
Cumulative prednisone ≥ 20 g (0, 1)	1.97 (1.14,3.40)*	2.49 (1.29, 4.82)**	2.96 (1.52, 5.73)***
Carotid Ultrasound			
Intima media thickness (per SD)	1.62 (1.30, 2.02)***	Not tested	1.31 (1.02, 1.70)*

[‡] 66 incident acute coronary syndromes occurred in 66 of 599 patients who have not experienced CV events previously. Variables measured at the first visit. SW = Stepwise; ESR = erythrocyte sedimentation rate; IMT = intima-media thickness. DAS28 = 28-joint disease activity score. DAS28 was tested separately in models that did not include tender or swollen joint counts, or ESR.

Values shown are hazard ratios (95% confidence intervals)

* P ≤ 0.05

**
 $P \leq 0.01$

 $P \leq 0.001$

Table 4

Bivariate and stepwise multivariable analyses of baseline factors associated with incident or recurrent acute coronary syndromes among 636 patients with RA who underwent carotid ultrasound[‡]

VARIABLE	Bivariate	SW Multivariable	
		Without IMT or past CV events	With IMT and past CV events
Demographics			
Age at first visit (per 10 years)	1.57 (1.36, 1.88)***	1.22 (1.03, 1.47)**	-
Men vs. Women	2.90 (1.81, 4.65)***	2.63 (1.66, 4.16)***	1.94 (1.11, 3.39)*
White vs. non-White	1.78 (1.12, 2.81)*	-	-
CV Risk Factors			
Diabetes mellitus (0, 1)	2.85 (1.61, 5.03)***	2.64 (1.64, 4.25)***	2.24 (1.44, 3.50)***
Hypercholesterolemia (0, 1)	2.05 (1.19, 3.52)**	-	-
Hypertension (0, 1)	2.39 (1.46, 3.52)***	1.94 (1.23, 3.08)**	1.56 (1.00, 2.44)*
Past smoking (0, 1)	1.99 (1.00, 3.97)*	-	-
Current smoking (0, 1)	1.78 (1.05, 3.02)*	-	-
Body mass index (Kg/M ²)	0.99 (0.97, 1.02)	-	-
RA Manifestations			
RA duration (per year)	1.03 (1.03, 1.05)*	1.02 (0.99, 1.04)	-
Tender joint count (per joint)	1.01 (0.99, 1.03)	-	-
Swollen joint count (per joint)	1.04 (0.99, 1.09)	1.03 (1.00, 1.06)*	1.03 (1.01, 1.06)**
Deformed joint count (per joint)	1.02 (0.99, 1.05)	-	-
Subcutaneous nodules (0, 1)	1.25 (0.76, 2.06)	-	-
Rheumatoid factor (0, 1)	1.65 (0.90, 3.03)	-	-
ESR (per 10 mm/hour)	1.06 (0.97, 1.18)	-	-
DAS 28 (per unit)	1.06 (0.90, 1.26)	-	-
RA Treatment			
Methotrexate (0, 1)	0.96 (0.59, 1.57)	-	-
Hydroxychloroquine (0,1)	0.94 (0.41, 2.11)	-	-
Cumulative prednisone ≥20 g (0, 1)	1.97 (1.14, 3.40)*	1.83 (1.08, 3.10)*	2.12 (1.32, 3.42)**
Atherosclerosis markers			
Past CV event (0, 1)	5.37 (3.42, 8.43)***	Not tested	2.87 (1.75, 4.73)***
Intima media thickness (per SD)	1.99 (1.65, 2.39)***	Not tested	1.61 (1.24, 2.08)**

[‡] 121 acute coronary syndromes occurred after enrollment among 84 of the 636 patients. Variables measured at the first visit.

[§] Confidence intervals estimated using robust standard errors to adjust for within-patient correlation.

RA = rheumatoid arthritis; SW= Stepwise; ESR = erythrocyte sedimentation rate; DAS28 = 28-joint disease activity score. DAS28 was tested separately in models that did not include tender or swollen joint counts, or ESR.

*
 $P \leq 0.05$

**
 $P \leq 0.01$

 $P \leq 0.001$