Title

Impact of Cumulative Inflammation, Cardiac Risk Factors, and Medication Exposure on Coronary Atherosclerosis Progression in Rheumatoid Arthritis

Journal

Arthritis & Rheumatology, 72(3)

ISSN

2326-5191

Authors

Karpouzas, George A
Ormseth, Sarah R
Hernandez, Elizabeth
et al.

Publication Date

2020-03-01

DOI

10.1002/art.41122

Peer reviewed

DR. GEORGE ATHANASIOS KARPOUZAS (Orcid ID : 0000-0003-1065-1563)

Article type : Full Length

Running title: predictors of coronary plaque progression in rheumatoid arthritis

Impact of cumulative inflammation, cardiac risk factors and medication exposure on coronary atherosclerosis progression in rheumatoid arthritis

George A Karpouzas MD[1], Sarah R Ormseth PhD[1], Elizabeth Hernandez MA[1], Matthew J Budoff MD[2]

[1]Division of Rheumatology, Harbor-UCLA Medical Center and Los Angeles Biomedical Research Institute, Torrance, CA, USA
[2]Division of Cardiology, Harbor-UCLA Medical Center and Los Angeles Biomedical Research Institute, Torrance, CA, USA

Correspondence to: George A Karpouzas, MD, 1124 West Carson Street, Building E4-R17, Torrance, CA 90502; gkarpouzas@labiomed.org; Tel: +1-310-222-8119.

Abstract word count: 250

Word count: 3,265 (4,200 max allowed)

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ART.41122

ABSTRACT

Objectives. To explore incidence and progression of coronary atherosclerosis and identify determinants thereof in patients with rheumatoid arthritis. We specifically evaluated the impact of inflammation, cardiac risk factors, duration of medication exposure and their interactions on coronary plaque progression.

Methods. One hundred-one participants with a baseline coronary computed tomography angiography underwent follow-up assessment in 83±3.6 months. Plaque burden was reported as segment involvement score (SIS) describing the number of coronary segments with plaque and segment stenosis score (SSS) characterizing the cumulative plaque stenosis over all evaluable segments. Plaque composition was defined as non-calcified (NCP), mixed (MP) or calcified (CP). Coronary artery calcium (CAC) was quantified by the Agatston method.

Results.

Total plaque increased in 48% of patients; progression was predicted by older age, higher cumulative inflammation and total prednisone dose ($p<0.05$). CAC progressors were older, more obese, hypertensive, with higher cumulative inflammation compared to non-progressors ($p<0.05$). Longer exposure to biologics associated with lower likelihood of NCP progression, lesion remodeling and constrained CAC change in patients without baseline calcification independently of inflammation, prednisone dose, or statin exposure (all $p<0.05$). Longer statin treatment further restricted NCP progression and attenuated the effect of inflammation on plaque and CAC increase ($p<0.05$). Stringent systolic blood pressure control further weakened the effect of inflammation on total plaque progression.

Conclusion. Inflammation was a consistent and independent predictor of coronary atherosclerosis progression in RA; it should therefore be specifically targeted towards mitigating cardiovascular risk. BDMARDs, statins and blood pressure control may further constrain plaque progression directly or indirectly.

Keywords: Rheumatoid arthritis, subclinical cardiovascular disease, atherosclerosis

Individuals with RA experience a higher rate of cardiovascular events (CVE) compared with controls (1). We recently reported greater prevalence, severity, burden, and vulnerability of occult coronary plaque in RA compared with age and gender-matched individuals without autoimmunity (2). Increasing atherosclerosis burden on serial CCTA is an independent predictor of acute coronary syndromes in both men and women without autoimmune disease (3,4). In contrast, stabilization in plaque size is associated with decreased risk of future CVE (5). Changes in coronary plaque load and composition in RA are largely unexplored. Two recent reports evaluated determinants of incident CAC or prevalent CAC progression and described associations with age, higher blood pressure and triglyceride levels but no disease-specific traits or treatments (6,7). However, CAC represents roughly 20% of total plaque burden in both RA and general patients and may not be present in earlier disease (2,8); more importantly, additional information on plaque burden, stenotic severity and composition exclusively rendered by CCTA significantly improves upon predictive value of CAC for CVE in general patients (9).

In the present study we explored incident coronary plaque rates, prevalent atherosclerosis progression and plaque composition change in a cohort of RA patients with baseline and follow-up CCTA. We further identified determinants of increasing plaque and CAC burden and specifically interrogated the role of cumulative inflammation, cardiac risk factors, RA-specific or ancillary medications and their interactions on plaque progression. We hypothesized that higher cumulative inflammation might predict greater coronary plaque load at follow-up; we further posited that duration of exposure to RA-specific medications such as glucocorticoids, conventional synthetic and biologic DMARDs (csDMARDs and bDMARDs respectively), traditional cardiac risk factors and statin treatments may exert opposing effects on plaque growth or composition.

MATERIALS AND METHODS

Patient Recruitment

One hundred-one patients who participated in a prior CCTA study of subclinical coronary atherosclerosis in RA (2) underwent follow-up assessments after 83±3.6 months. Participants had been prospectively followed at our outpatient rheumatology clinic since 2010 to 2011 (baseline visit). Inclusion and exclusion criteria have been described in detail elsewhere (2). Briefly, patients were enrolled if they met the 2010 classification criteria for RA, were ≥18 years of age and had no symptoms or history of cardiovascular disease at baseline. Major exclusion criteria were concomitant autoimmune syndromes except for Sjogren's Syndrome, weight >325 pounds (147.7 kg), iodine allergy, glomerular filtration rate <60ml/min, malignancy, and chronic or active infections. The study was approved by the local Institutional Review Board and signed informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Predictor variables

Hypertension constituted SBP ≥140mmHg or DBP ≥90mmHg or antihypertensive use. Diabetes mellitus encompassed HgbA1c>6.5%, or hypoglycemic medication use. Hyperlipidemia was defined as fasting cholesterol >200 mg/dl, or LDL>130 mg/dl or statin use. Smoking entailed cigarette consumption within 30 days from screening. Waist-to-height ratio (WHtR) was used as a measurement of central obesity (10). Screening for incident cardiac risk factors was conducted according to EULAR recommendations for CV risk assessment. Disease activity was evaluated by 28-joint counts and c-reactive protein (DAS28-CRP) at every clinic visit (11). Cumulative inflammatory burden was calculated as a time-averaged CRP spanning all visits between baseline and follow-up scans (12). Medications were reconciled at every clinic visit; including use and doses of prednisone, conventional synthetic disease modifying antirheumatic drugs (csDMARDs), bDMARDs and statins. Total prednisone and methotrexate doses from baseline to follow-up were calculated; years exposure to bDMARD and statins were also estimated.

Laboratory evaluations

Complete blood counts, comprehensive metabolic panels, erythrocyte sedimentation rate (ESR) and CRP were completed on the day of both CCTA assessments as well as on

every clinic visit in-between scans. Fasting lipid evaluations were carried out on the days of both scans as well as according to EULAR recommendations for CV risk assessment in-between scans (11).

Multi-Detector Coronary Computed Tomography Angiography (CCTA)

Baseline scans were performed with a 64-multidetector row Lightspeed VCT scanner (GE Healthcare) between 3/2010-3/2011; follow-up scans were carried out in a 256-multidetector row scanner between 3/2017-3/2018. Baseline and follow-up images were analyzed in the same campaign and in random order by a single, blinded interpreter (MJB) (13). CAC was quantified by the Agatston method (14). Coronary arteries were evaluated on contrast-enhanced scans using a standardized 17-segment American Heart Association model (15). For longitudinal comparisons, baseline and follow-up coronary segments were coaligned using fixed anatomic landmarks as fiducial points. Each segment was scored for stenosis severity on a 0 to 4 scale based on grade of luminal restriction, where 0 = 0% (absence of plaque), 1 = 1-29% stenosis, 2 = 30-49% stenosis, 3 = 50-69% stenosis, and 4 = >70% (2). Plaque composition was defined as non-calcified (NCP), mixed (MP), or calcified (CP) as reported elsewhere (16). Subjects received two individual quantitative scores (16); segment involvement score (SIS) represented the total number of segments with plaque; segment stenosis score (SSS) described the cumulative stenosis grade rendered by plaque in all evaluable segments. Reproducibility of these scoring measures for our institution has been previously reported (16).

Outcome variables

Changes in burden of total plaque, specific plaque types (NCP, MP, CP) and CAC constituted the primary outcome variables. Atherosclerosis progression was defined as the number of new segments with any plaque per patient (SIS increase, range 0-17) or rise in stenotic plaque severity in all evaluable coronary segments with plaque (SSS increase, range 0-68). CAC progresion was expressed as the absolute difference between the second and first measurement of coronary artery calcium [$CAC_{(follow\text{-}up)} - CAC_{(baseline)}$].

Statistical analysis

Continuous variables were expressed as means with 95% confidence intervals (CI) or standard deviations (SD) unless otherwise described; categorical variables were expressed as numbers with percentages. Negative binomial regression was used to assess count outcomes (SIS and SSS increase), robust logistic regression for dichotomous outcomes (NCP, MP, and CP progression), and generalized linear models with a Tweedie (Poisson-Gamma) error distribution and log link function for CAC change. For each outcome, univariable models with candidate predictors were estimated, followed by multivariable models constructed via a backward elimination variable selection process. The backward selection process started with all predictors associated with the outcome in univariable analyses at the level of $P<0.20$ and sequentially removed variables with $P>.10$, beginning with the least significant variable. For primary outcomes, the possible presence of interactions between cumulative inflammation and traditional risk factors was tested by introducing into the adjusted multivariable models the product of time-averaged CRP with each CV risk factor and medication exposure variable. Age and the time between scans were included as covariates in all models. Analyses were carried out in SPSS.

RESULTS

Participants were predominantly female with established, seropositive, erosive, and well-controlled disease (Table 1). Follow-up included an average of nineteen visits over seven years. Forty-eight patients were considered plaque progressors based on either displaying new coronary segments with plaque (SIS change range 0-6) or increased stenotic severity in segments with prior plaque (SSS change range 0-9). Clinical characteristics of progressors and non-progressors are presented in table 1; RA-related parameters and treatments were similarly distributed across both groups including time on csDMARDs, bDMARDs, total prednisone and methotrexate doses. Although progressors were older, more obese, hypertensive and with higher time-averaged SBP compared to non-progressors, those differences were no longer significant after adjusting for age. Progressors more commonly had plaque and CAC, as well as higher plaque and CAC scores at baseline

(p<0.05). Eight incident CVE occurred throughout the observation period (supplementary table 1); four were ischemic and 4 non-ischemic. All patients with events remained in the study and were included in the analysis.

Incident plaque rates, plaque progression and calcification over time

Seventy patients (69.3%) displayed coronary plaque at baseline. Incident plaque rate (SIS>0 at follow-up in patients with baseline SIS=0) was 4.7 (95% CI 2.2-8.6)/100 PY; in patients with prevalent atherosclerosis (baseline SIS>0) plaque progressed at a rate of 7.8 (95% CI 5.5-10.7)/100 PY. CAC progression rate was 6.0 (95% CI 4.3 to 8.1)/100 PY; it increased at a median of 15.1 (95% CI 9.3 to 32.6) Agatston units/year in patients with prevalent CAC. Patients with incident CAC demonstrated a median annualized progression rate of 1.7 (95% CI 0.8 to 4.1) units. Quantitative changes for total plaque as well as all three plaque subtypes are shown in supplementary table 2. Overall, total plaque burden and coronary calcification scores increased ($p \leq 0.012$); additionally, 9 patients exhibited NCP progression, 21 had MP progression and 35 showed CP increase.

Changes in coronary plaque composition

At baseline, 187 coronary segments with plaque were identified in 70 patients. At follow-up, 97 new lesions appeared in segments without plaque initially; 15 new plaques were identified in 10 (9.9%) patients without plaque at baseline, while 82 new plaques were identified in 37 (36.6%) patients with prevalent plaque. Of the 97 incident plaques at follow-up 20 were NCP, 21 MP and 56 were CP. Figure 1 delineates per-plaque composition changes from baseline to follow-up.

Determinants of change in coronary atherosclerosis burden

Older age, higher TA-CRP and greater total prednisone dose independently predicted both SIS increase as well as SSS increase in multivariate models (Table 2). The effect of TA-CRP on total plaque increase was modified by statin use, since TA-CRP predicted SIS increase only in patients unexposed to statins or receiving statins <50% of the study period, but not those receiving statins >50% of the time [p for interaction = 0.017, Figure 2A).

CAC change was independently predicted by age, obesity, TA-CRP, and total prednisone dose (Table 2). Statin exposure also modified the effect of TA-CRP on CAC change; specifically, higher TA-CRP significantly associated with CAC change only in statin-unexposed patients but not those with any statin exposure during the study period (P for interaction = 0.006, Figure 2B). Additionally, the effect of TA-CRP on CAC change was moderated by TA-SBP; specifically, TA-CRP significantly predicted CAC change for patients in the middle (126<TA SBP<138mmHg) and highest (TA-SBP>138mmHg) tertiles but not those in the lowest tertile of TA-SBP (P for interaction = 0.023, Figure 2C).

CAC change was further assessed separately in patients with and without detectable baseline CAC in a supplementary analysis due to a significant interaction between baseline CAC and bDMARD duration (P for interaction = 0.001). In a model adjusting for age, obesity, TA-CRP, and total prednisone dose, longer bDMARD exposure negatively associated with CAC change in patients without baseline CAC (OR=0.77 [95% CI 0.60, 0.98], P=0.031) but not those with prevalent CAC (OR=1.08 [95% CI 0.94, 1.23], P=0.28). Baseline CAC presence did not modify the effects of the other primary predictors on CAC change (data not shown).

Determinants of plaque progression by subtype (NCP, MP, CP) are displayed in table 3. Both longer bDMARD treatment and exposure to statins independently associated with a decreased likelihood of NCP progression; inclusion of total prednisone and methotrexate dose in the model did not affect results (data not shown). Older age fostered both MP and CP plaque progression; Increased CP burden further associated with hypertension, obesity and higher cumulative inflammation.

DISCUSSION

This is the first study exploring predictors of coronary plaque progression in a well characterized, prospective cohort of RA patients without known cardiovascular disease and a long-term follow-up. We specifically interrogated the effects of cumulative inflammation, traditional cardiac risk factors, RA-specific and ancillary therapies and their interactions on

progression of total plaque, various plaque subtypes and coronary calcification. Our findings, therefore, complement and enrich prior reports on CAC progression in RA (6,7).

We report several novel findings: First, higher cumulative inflammation was a consistent and independent predictor of total coronary plaque progression in RA; this included new segments with plaque on follow-up, as well as greater stenosis severity in segments with plaque at baseline. This is consistent with two prior reports that higher inflammatory burden was associated with carotid plaque progression in RA (17,18). Our observation, however, is of unique significance since the presence of carotid plaque in inflammatory joint diseases- including RA- do not sufficiently identify patients with coronary artery disease and since quantitative measurements of carotid atherosclerosis do not correlate with presence or burden of coronary plaque (19). We used time-averaged CRP as a surrogate of cumulative inflammation; in supplementary analyses similar results were observed using time-averaged swollen joint counts as a predictor, but not when time-averaged tender joint counts, time-averaged patient global assessments (PGA) or composite indices such as DAS28-CRP or CDAI were used. Importantly, higher cumulative inflammation in RA, was associated with greater future CVE risk (20), while reduction in time-averaged inflammation yielded lower CVE risk (21). Since atherosclerosis progression on serial CCTA independently predicted CVE in general patients (3,5), our observations collectively reaffirm that stringent and durable control of inflammation should be a primary objective in our quest to mitigate cardiovascular risk in RA.

Second, higher cumulative inflammation may additionally promote plaque remodeling and maturation as evidenced by its strong association with CAC and CP progression. Indeed, 56 of 117 (48%) segments with CP at follow-up had no plaque at baseline; ostensibly, incident plaques appeared in those segments as NCPs that grew and matured over periods of inflammation during disease flares. As inflammation subsided, they eventually transitioned to advanced, heavily CP. Support for this timeline was provided in supplementary analyses, where we demonstrated that the within-patient variability in CRP over time significantly predicted CAC progression independently of age, hypertension, obesity and baseline CAC ($p=0.018$). Concordantly, previous reports confirmed that in early

atherogenesis inflammation drives and co-localizes with initial intimal calcification (22); in response to proinflammatory cytokine production by macrophages at sites of lipid accumulation, vascular smooth muscle cells (VSMC) undergo apoptosis, release extracellular vesicles secondary to stress, or undergo phenotype transition to osteoblastic cells, as a self-preservation strategy. All those events associate with local calcification, which is initially undetectable on CCTA (22). If inflammation persists, macrophage infiltration and microcalcifications progress, eventually appearing as spotty calcifications on CCTA. If inflammation subsides and the VSMC repair system is not overwhelmed (cells do not die by apoptosis in the meantime), this process will lead to calcified acellular plaques. Indeed, in advanced plaques, large, dense calcifications are spatially distinct from macrophages, inversely correlate with macrophage burden and- like the calcific mummification of soft tissue infections- represent healing that stabilizes the arterial wall (22). Hence, higher burden of CP at follow-up may reflect the final stage in the life cycle of plaques that appeared and evolved in the context of a historically higher inflammatory load. Curiously, this association between inflammation and calcification was not observed in prior reports of CAC progression in RA (6,7). One potential explanation may be the longer duration of follow-up (7 years compared to ≤3 years) and greater number of evaluation points (19 compared to 2 or 3) in our study (6,7), allowing for a more comprehensive assessment of inflammation variability as well as adequate time for plaque remodeling thereof.

Our third novel finding is that longer bDMARD exposure may yield an atheroprotective effect in RA, independently of stringent control of systemic inflammation; specifically, lengthier bDMARD experience reduced the likelihood of NCP progression, the earliest histologically atherosclerotic lesion discernible on CCTA. Biologic therapies were similarly shown to selectively influence lipid-rich, soft plaque volume in patients with psoriasis (23). Moreover, we showed that lengthier bDMARD exposure appeared to prevent maturation and remodeling of such plaques, as evidenced by the lower risk of progressive calcification, independently of inflammation, duration of statin exposure and total prednisone dose. In a similar fashion, bDMARDs have been shown to inhibit radiographic progression in RA regardless of attainment of optimal disease control (24–26). By contrast, neither duration

of exposure to csDMARDs nor total methotrexate dose in our study influenced coronary plaque progression.

Fourth, we established an independent coronary atheroprotective effect of statins in RA; longer statin exposure associated with lower risk of NCP progression regardless of cumulative inflammation, total prednisone and methotrexate dose or bDMARD duration. Indeed, stabilization or reduction in plaque size, particularly the non-calcific lipid core component, is well documented in response to high intensity statin therapy in general patients (27–30) and related to lower risk of CVE (5). However, the atheroprotective effect of statin in our study was not related to the treatment intensity but rather the duration of the exposure. Our additional observation that the duration of statin exposure moderated the effect of cumulative inflammation on both plaque and CAC progression, highlights potential local anti-inflammatory effects of statins at the plaque level (31), independently of systemic inflammation as reflected by blood CRP levels (32).

Regrettably, sustained remission may be unrealistic for the majority of patients at the present time (33). Could RA-specific or other ancillary treatments mitigate coronary plaque progression in subjects who do not achieve stringent inflammatory control? We observed that longer statin exposure additionally moderated the effect of inflammation on total plaque progression; in patients treated with statins>50% of the observation time, higher time-averaged CRP failed to yield significant progression of either coronary plaque or CAC. We further noted that durable, aggressive systolic blood pressure (SBP) control throughout the observation period may be instrumental, particularly in the face of chronic residual inflammation; time-averaged SBP at the lowest tertile (<126mmHg) attenuated the effect of higher cumulative inflammation on CAC progression whereas higher measurements significantly accelerated it. Nevertheless, it is currently unclear whether atheroprotection in RA- specifically in the context of residual inflammation- requires adjustment of the recommendations for starting lipid lowering therapy or adoption of more rigorous SBP targets than in general patients (34).

We additionally demonstrated that cumulative prednisone dose adversely affected total coronary plaque as well as CAC progression independently of cumulative inflammation

or cardiac risk factors. Despite the fact that physicians generally prescribe corticosteroids to patients with higher disease activity, our observation highlights the true deleterious effect of corticosteroids on the vascular wall rather than confounding by indication. Importantly, the duration of statin exposure in our study did not moderate this effect of total prednisone dose on coronary plaque progression, as previously reported for carotid atherosclerosis (17). Since higher cumulative prednisone dose has been linked to greater incidence of CVE in RA (35), timely de-escalation and withdrawal may be warranted.

Our study has certain limitations. First, the absence of a control group hinders us from determining whether the observed magnitude and predictors of plaque change in RA are different from subjects without autoimmunity. However, at least for CAC, where a precedent for comparison exists, the observed CAC progression in our patients was significantly higher than predicted based on age, gender, and ethnicity-matched reference values (relative risk, 2.21; 95% confidence interval 1.39 to 3.52, p=0.001) (36). Second, our patients had low cumulative inflammatory burden; 47% had time-averaged DAS28-CRP<2.4 and 68% had DAS28-CRP<2.8. Moreover, rigorous screening and management of incident cardiac risk factors occurred for all patients during their clinic visits. Additionally, patients with prevalent calcification or significant plaque burden on baseline CCTA were given at least statin therapy, if not more aggressive treatment for atherosclerosis and regardless of such requirement on clinical grounds. Consequently, the likelihood of plaque progression may have been attenuated in patients who were otherwise poised to exhibit the greatest increase. Accordingly, the proportions, magnitude of plaque progression and effect sizes of predictors thereof may have been attenuated compared to cohorts with higher disease activity or untreated risk factors.

Conclusion

Occult coronary atherosclerosis burden increased in a significant proportion of patients with RA. Cumulative inflammatory burden and total prednisone dose were disease specific, independent determinants of plaque progression. Our findings confirm the importance of prioritizing and targeting durable control of inflammation in RA. Longer exposure to biologics or statins as well as rigorous control of systolic blood pressure may

further moderate the effect of inflammation on atherosclerosis progression and yield additional coronary atheroprotective effects beyond optimal control of systemic inflammation.

ACKNOWLEDGMENTS

The authors would like to thank Drs. Benedict Chou and Gopika Miller for assistance with formalized clinical assessments and Ms. Lorena Ruiz for facilitation of study coordination. We would further like to express our gratitude to the patients participating in the study.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content and all authors approved the final version to be published. Dr Karpouzas had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Karpouzas, Budoff

Acquisition of Data. Karpouzas, Ormseth, Hernandez, Budoff

Analysis and interpretation of the data. Karpouzas, Ormseth, Hernandez, Budoff

ROLE OF THE STUDY SPONSOR

This work was supported by Pfizer through an investigator-initiated grant award to GAK - ASPIRE grant (WI215017). Pfizer provided funding for the study. The sponsor was not involved in the study design, study related procedures or manuscript drafting. The authors independently collected the data, interpreted the results and had the final decision to submit the manuscript for publication.

REFERENCES

1. Naranjo A, Sokka T, Descalzo MA, Calvo-Alén J, Hørslev-Petersen K, Luukkainen RK, et al. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. *Arthritis Res Ther* 2008;10:R30.

2. Karpouzas GA, Malpeso J, Choi T-Y, Li D, Munoz S, Budoff MJ. Prevalence, extent and composition of coronary plaque in patients with rheumatoid arthritis without symptoms or prior diagnosis of coronary artery disease. *Ann Rheum Dis* 2014;73:1797–804.

3. Motoyama S, Ito H, Sarai M, Kondo T, Kawai H, Nagahara Y, et al. Plaque Characterization by Coronary Computed Tomography Angiography and the Likelihood of Acute Coronary Events in Mid-Term Follow-Up. *J Am Coll Cardiol* 2015;66:337–46.

4. Gu H, Gao Y, Wang H, Hou Z, Han L, Wang X, et al. Sex differences in coronary atherosclerosis progression and major adverse cardiac events in patients with suspected coronary artery disease. *J Cardiovasc Comput Tomogr* 2017;11:367–72.

5. Inoue K, Motoyama S, Sarai M, Sato T, Harigaya H, Hara T, et al. Serial coronary CT angiography-verified changes in plaque characteristics as an end point: evaluation of effect of statin intervention. *JACC Cardiovasc Imaging* 2010;3:691–8.

6. Chung CP, Giles JT, Kronmal RA, Post WS, Gelber AC, Petri M, et al. Progression of coronary artery atherosclerosis in rheumatoid arthritis: comparison with participants from the Multi-Ethnic Study of Atherosclerosis. *Arthritis Res Ther* 2013;15:R134.

7. Udachkina HV, Novikova DS, Popkova TV, Kirillova IG, Markelova EI. Dynamic of changes in coronary artery calcification in early rheumatoid arthritis patients over 18 months. *Rheumatol Int* 2018;38:1217–24.

8. Leschka S, Seitun S, Dettmer M, Baumüller S, Stolzmann P, Goetti R, et al. Ex vivo evaluation of coronary atherosclerotic plaques: characterization with dual-source CT in comparison with histopathology. *J Cardiovasc Comput Tomogr* 2010;4:301–8.

9. Hou Z, Lu B, Gao Y, Jiang S, Wang Y, Li W, et al. Prognostic value of coronary CT angiography and calcium score for major adverse cardiac events in outpatients. *JACC Cardiovasc Imaging* 2012;5:990–999.

10. Swainson MG, Batterham AM, Tsakirides C, Rutherford ZH, Hind K. Prediction of whole-body fat percentage and visceral adipose tissue mass from five anthropometric variables. *PloS One* 2017;12:e0177175.
11. Peters MJ, Symmons DP, McCarey D, Dijkmans B, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010;69:325–31.
12. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *BMJ* 1990;300:230–5.
13. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol* 2008;52:1724–32.
14. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827–32.
15. Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr* 2014;8:342–58.
16. Pagali SR, Madaj P, Gupta M, Nair S, Hamirani YS, Min JK, et al. Interobserver variations of plaque severity score and segment stenosis score in coronary arteries using 64 slice multidetector computed tomography: a substudy of the ACCURACY trial. *J Cardiovasc Comput Tomogr* 2010;4:312–8.
17. Giles JT, Post WS, Blumenthal RS, Polak J, Petri M, Gelber AC, et al. Longitudinal predictors of progression of carotid atherosclerosis in rheumatoid arthritis. *Arthritis Rheum* 2011;63:3216–25.

18. Im, CH, Kwon, SH, Eun, JS, Kim, NR, Nam, EJ, Kang, YM. Inflammatory Burden Predicts Carotid Plaque Progression and Subsequent Cardiovascular Events In Rheumatoid Arthritis: The 2-year Prospective Cohort Study . *Arthritis Rheum* 2013;65:S155.
19. Svanteson M, Rollefstad S, Kløw NE, Hisdal J, Ikdahl E, Semb AG, et al. Associations between coronary and carotid artery atherosclerosis in patients with inflammatory joint diseases. *RMD Open* 2017;3. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5604717/. Accessed March 16, 2019.
20. Innala L, Möller B, Ljung L, Magnusson S, Smedby T, Södergren A, et al. Cardiovascular events in early RA are a result of inflammatory burden and traditional risk factors: a five year prospective study. *Arthritis Res Ther* 2011;13:R131.
21. Solomon DH, Reed GW, Kremer JM, Curtis JR, Farkouh ME, Harrold LR, et al. Disease activity in rheumatoid arthritis and the risk of cardiovascular events. *Arthritis Rheumatol Hoboken NJ* 2015;67:1449–55.
22. Aikawa E, Nahrendorf M, Figueiredo J-L, Swirski FK, Shtatland T, Kohler RH, et al. Osteogenesis associates with inflammation in early-stage atherosclerosis evaluated by molecular imaging in vivo. *Circulation* 2007;116:2841–50.
23. Elnabawi YA, Dey AK, Goyal A, Groenendyk JW, Chung JH, Belur AD, et al. Coronary artery plaque characteristics and treatment with biologic therapy in severe psoriasis: results from a prospective observational study. *Cardiovasc Res* 2019.
24. Døhn UM, Ejbjerg B, Boonen A, Hetland ML, Hansen MS, Knudsen LS, et al. No overall progression and occasional repair of erosions despite persistent inflammation in adalimumab-treated rheumatoid arthritis patients: results from a longitudinal comparative MRI, ultrasonography, CT and radiography study. *Ann Rheum Dis* 2011;70:252–8.
25. Smolen JS, Avila JCM, Aletaha D. Tocilizumab inhibits progression of joint damage in rheumatoid arthritis irrespective of its anti-inflammatory effects: disassociation of the link between inflammation and destruction. *Ann Rheum Dis* 2011;71:687–93.
26. Smolen JS, Han C, Bala M, Maini RN, Kalden JR, Heijde D van der, et al. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor

necrosis factor trial in rheumatoid arthritis with concomitant therapy study. *Arthritis Rheum* 2005;52:1020–30.
27. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA* 2006;295:1556–65.
28. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, et al. Effect of two intensive statin regimens on progression of coronary disease. *N Engl J Med* 2011;365:2078–87.
29. Puri R, Nicholls SJ, Shao M, Kataoka Y, Uno K, Kapadia SR, et al. Impact of statins on serial coronary calcification during atheroma progression and regression. *J Am Coll Cardiol* 2015;65:1273–82.
30. Räber L, Taniwaki M, Zaugg S, Kelbæk H, Roffi M, Holmvang L, et al. Effect of high-intensity statin therapy on atherosclerosis in non-infarct-related coronary arteries (IBIS-4): a serial intravascular ultrasonography study. *Eur Heart J* 2015;36:490–500.
31. Martín-Ventura JL, Blanco-Colio LM, Gómez-Hernández A, Muñoz-García B, Vega M, Serrano J, et al. Intensive treatment with atorvastatin reduces inflammation in mononuclear cells and human atherosclerotic lesions in one month. *Stroke* 2005;36:1796–800.
32. Tawakol A, Fayad ZA, Mogg R, Alon A, Klimas MT, Dansky H, et al. Intensification of statin therapy results in a rapid reduction in atherosclerotic inflammation: results of a multicenter fluorodeoxyglucose-positron emission tomography/computed tomography feasibility study. *J Am Coll Cardiol* 2013;62:909–17.
33. Einarsson JT, Willim M, Ernestam S, Saxne T, Geborek P, Kapetanovic MC. Prevalence of sustained remission in rheumatoid arthritis: impact of criteria sets and disease duration, a Nationwide Study in Sweden. *Rheumatol Oxf Engl* 2019;58:227–36.
34. Hollan I, Dessein PH, Ronda N, Wasko MC, Svenungsson E, Agewall S, et al. Prevention of cardiovascular disease in rheumatoid arthritis. *Autoimmun Rev* 2015;14:952–69.

35. Evans MR, Escalante A, Battafarano DF, Freeman GL, O'Leary DH, Rincón I del. Carotid atherosclerosis predicts incident acute coronary syndromes in rheumatoid arthritis. *Arthritis Rheum* 2011;63:1211–20.
36. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2006;113:30–7.

TABLES AND FIGURES

Table 1. Baseline clinical characteristics. Values represent Mean (SD) or number (%). RF: Rheumatoid factor, ACPA: anti-cyclic citrullinated peptide antibodies, CRP: high-sensitivity c-reactive protein, SJC: swollen joint count, DAS28-CRP: disease activity score, LDL: low-density lipoprotein, cs-DMARD: conventional synthetic disease modifying anti-rheumatic drug, bDMARD: biologic disease modifying anti-rheumatic drug, SIS: segment involvement score, SSS: segment stenosis score, NCP: non-calcified plaque, MP: mixed plaque, CP: calcified plaque *p<0.05 for progressors vs. non-progressors, § number (n=49) of patients exposed to prednisone at anytime between baseline and follow-up scans, ¶ number (n=78) of patients exposed to bDMARDs at anytime between baseline and follow-up scans, † number (n=59) of patients exposed to statin at anytime between baseline and follow-up scans.

Table 2. Predictors of total coronary plaque progression in RA.
SIS: segment involvement score, SSS: segment stenosis score, CAC: coronary artery calcium, 95% CI: 95% confidence interval. †p<0.1, *p<0.05, **p<0.01, ***p<0.001. Model 1: adjusted for time in-between scans and baseline plaque burden values, Model 2: additional adjustments for all variables in the final multivariable model selected using backwards selection.

Table 3. Predictors of change in atherosclerosis burden by plaque type in RA.

OR: odds ratio, 95% CI: 95% confidence interval. †p<0.1, *p<0.05, **p<0.01, ***p<0.001. Model 1: adjusted for age and time in-between scans, Model 2: additional adjustments for all variables in the final multivariable model selected using backwards selection

Figure 1. Change in plaque composition, new and disappearing plaques from baseline to follow-up. NCP: non-calcified plaque, MP: mixed plaque, CP: calcified plaque, DP: disappearing plaque, NP: new plaque.

Figure 2. Duration of statin exposure and blood pressure control moderate the effect of cumulative inflammation on coronary plaque progression in RA. **A.** Higher time-averaged CRP yielded significant plaque progression in patients not on statin treatment [RR=1.48 (1.05-2.09), p=0.025] and those receiving statins< 50% of the study observation period [RR=1.31 (1.01-1.69), p=0.040]. In contrast, no such risk was observed in subjects with statin exposure>50% of study time [RR=1.07 (0.93-1.22), p=0.35]; p-interaction=0.017. **B.** Higher time-averaged CRP rendered high CAC progression risk in statin-naïve patients [OR=2.33 (1.29-4.22), p=0.005]; in contrast, any statin exposure mitigated that risk [OR=1.17 (0.81-1.68, p=0.410), p=0.98 for statin exposure<50% and OR=0.96 (0.44-2.17), p=0.98 for statin exposure>50%]; p-interaction=0.006. Both statin interaction models reported in panels A and B are adjusted for age, dyslipidemia, cumulative prednisone dose, total methotrexate dose and bDMARD duration. **C.** Higher time-averaged CRP predicted significant CAC progression in subjects in the middle (126<SBP<138mmHg) and highest (SBP>138mmHg) tertiles of time-averaged SBP [OR=1.68 (1.14-2.47), p=0.009 and OR=2.39 (1.52-3.77), p<0.001 respectively] but not those in the lowest (SBP<126mmHg) tertile [OR=1.03 (0.61-1.74), p=0.92].

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Incident cardiovascular events in RA patients NICM: non-ischemic cardiomyopathy, HFrEF: Heart failure with reduced ejection fraction, STEMI: ST-segment elevation myocardial infarction, PCI: percutaneous intervention, HFpEF: Heart failure with preserved ejection fraction, LVDD: Left ventricular diastolic dysfunction, PAD: peripheral arterial disease.

Supplementary Table 2. Changes in coronary atherosclerosis burden from baseline to follow-up scan.

Table 1. Baseline Clinical Characteristics

	No Plaque Progression(n=53)	Plaque Progression (n=48)	Total Sample (N=101)
Age (years)*	48.07 ±9.88	55.19 ±9.49	51.45 ±10.29
Female	46 (86.79)	41 (85.42)	87 (86.14)
Follow-up duration (years)	7.00 ±0.33	6.94 ±0.34	6.97 ±0.33
Number of visits	18.83 ±3.49	18.46 ±4.18	18.65 ±3.82
RA-related parameters			
RA duration (years)	9.18 ±6.28	11.36 ±7.98	10.22 ±7.19
RF-positive	48 (90.57)	43 (89.58)	91 (90.10)
ACPA-positive	47 (88.68)	40 (83.33)	87 (86.14)
Erosions	33 (62.26)	31 (64.58)	64 (63.37)
Time-averaged CRP (mg/dl)	0.79 ±0.53	0.99 ±1.16	0.89 ±0.89
Time-averaged SJC	1.83 ±1.92	2.40 ±2.84	2.10 ±2.41
Time-averaged DAS28 CRP	2.69 ±0.80	2.70 ±0.90	2.69 ±0.84
Cardiovascular risk factors			
Hypertension at baseline*	16 (30.19)	29 (60.42)	45 (44.55)
Time-averaged SBP (mmHg)*	127.83 ±13.11	133.08 ±11.41	130.32 ±12.55
Time-averaged DBP (mmHg)	71.97 ±7.05	72.21 ±6.56	72.08 ±6.79
Dyslipidemia at baseline	25 (47.17)	26 (54.17)	51 (50.50)
Time-averaged LDL(mg/dl)	101.78 ±23.38	109.84 ±35.30	105.61 ±29.77
Diabetes at baseline	5 (9.43)	9 (18.75)	14 (13.86)
Current smoking	4 (7.55)	4 (8.33)	8 (7.92)
Waist-to-height ratio*	57.82 ±6.83	61.20 ±7.78	59.42 ±7.46
Medication at baseline			
Prednisone use	12 (22.64)	19 (39.58)	31 (30.69)
N-concomitant csDMARD	1.90 ±0.78	1.87 ±0.79	1.89 ±0.78
bDMARD use	34 (64.15)	30 (62.50)	64 (63.37)
Statin use at baseline	20 (37.74)	21 (43.75)	41 (40.59)
Medication during follow-up			
Cum. prednisone (grams)§	2.34 ±4.49	4.12 ±6.35	3.19 ±5.50
Cum. Methotrexate (grams)	36.01 ±18.04	38.81 ±18.52	37.34 ±18.23
bDMARD duration (years)¶	4.36 ±2.88	4.24 ±3.01	4.30 ±2.93

Statin duration (years)†*	1.83 ±2.58	3.04 ±2.82	2.41 ±2.75
Baseline plaque burden			
SIS total*	0.94 ±0.97	2.88 ±2.76	1.86 ±2.24
SSS total*	1.04 ±1.11	4.46 ±5.11	2.66 ±3.98
NCP>0	29 (54.72)	31 (64.58)	60 (59.41)
MP>0*	4 (7.55)	20 (41.67)	24 (23.76)
CP>0*	3 (5.66)	16 (33.33)	19 (18.81)
CAC>0*	5 (9.43)	26 (54.17)	31 (30.69)
Agatston score*	8.85 ±53.49	135.29 ±397.36	68.94 ±282.35

Values represent Mean (SD) or number (%). RF: Rheumatoid factor, ACPA: anti-cyclic citrullinated peptide antibodies, CRP: high-sensitivity c-reactive protein, SJC: swollen joint count, DAS28-CRP: disease activity score, LDL: low-density lipoprotein, cs-DMARD: conventional synthetic disease modifying anti-rheumatic drug, bDMARD: biologic disease modifying anti-rheumatic drug, SIS: segment involvement score, SSS: segment stenosis score, NCP: non-calcified plaque, MP: mixed plaque, CP: calcified plaque *$p<0.05$ for progressors vs. non-progressors, § number (n=49) of patients exposed to prednisone at anytime between baseline and follow-up scans, ¶ number (n=78) of patients exposed to bDMARDs at anytime between baseline and follow-up scans, † number (n=59) of patients exposed to statin at anytime between baseline and follow-up scans.

Table 2. Predictors of total coronary plaque progression in RA

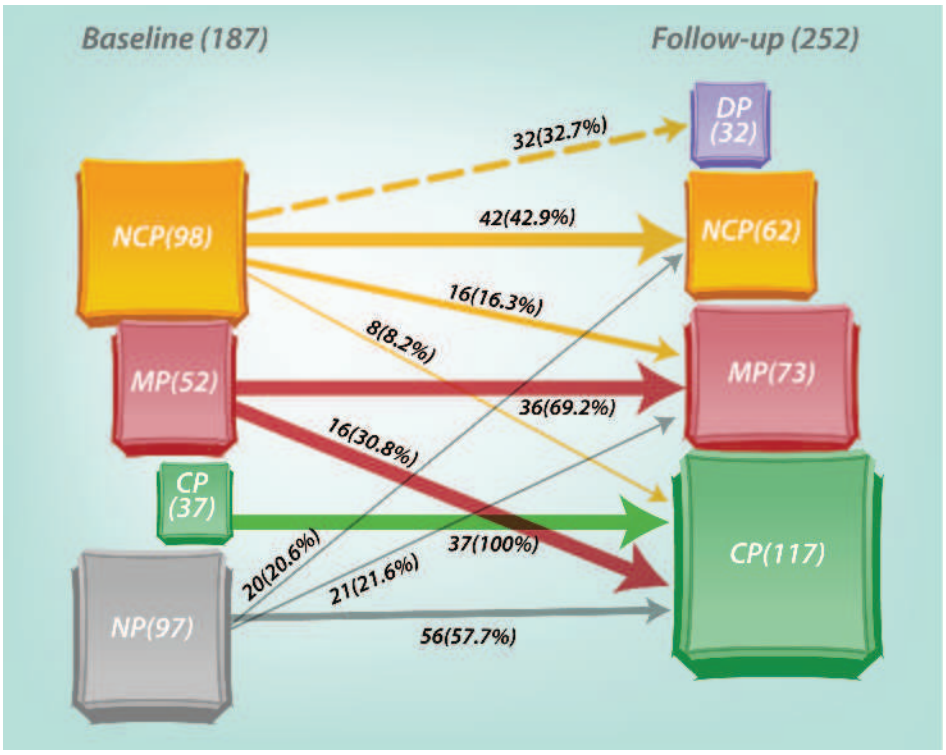
	SIS Increase		SSS Increase		CAC Increase	
	Univariable	Multivariable	Univariable	Multivariable	Univariable	Multivariable
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Age (years)		1.06 (1.03-1.09)***		1.05 (1.02-1.08)**		1.17 (1.09-1.26)***
Sex (male)	1.05 (0.38-2.90)		1.04 (0.43-2.52)		1.05 (0.38-2.90)	
Hypertension	1.74 (0.92-3.31)†		1.61 (0.90-2.90)		2.54 (1.19-5.42)**	2.58 (0.99-6.78)†
Dyslipidemia	0.74 (0.41-1.33)		0.94 (0.54-1.62)		1.17 (0.59-2.32)	
Diabetes	1.06 (0.45-2.51)		1.36 (0.63-2.94)		0.96 (0.39-2.37)	
Waist-to-height ratio	1.03 (1.00-1.07)†		1.02 (0.98-1.06)		1.07 (1.03-1.11)**	1.17 (1.02-1.34)*
Time-averaged CRP (mg/dL)	1.64 (1.36-1.98)***	1.42 (1.13-1.78)**	1.52 (1.23-1.88)***	1.35 (1.08-1.70)**	1.65 (1.34-2.03)***	1.64 (1.14-2.35)**
Statin duration (years)	1.05 (0.95-1.16)		1.04 (0.94-1.15)		1.14 (1.03-1.26)**	
bDMARD duration (years)	1.05 (0.97-1.14)		1.03 (0.94-1.12)		1.09 (0.96-1.23)	
Cum. methotrexate (grams)	1.01 (0.99-1.02)		1.00 (0.99-1.02)		1.01 (0.99-1.03)	
Cum. prednisone (grams)	1.09 (1.05-1.13)***	1.06 (1.02-1.10)**	1.08 (1.05-1.12)***	1.06 (1.02-1.10)**	1.07 (1.04-1.11)***	1.10(1.01-1.21)*

SIS: segment involvement score, SSS: segment stenosis score, CAC: coronary artery calcium, 95% CI: 95% confidence interval. †p<0.1, *p<0.05, **p<0.01, ***p<0.001. Model 1: adjusted for time in-between scans and baseline plaque burden values, Model 2: additional adjustments for all variables in the final multivariable model selected using backwards selection.

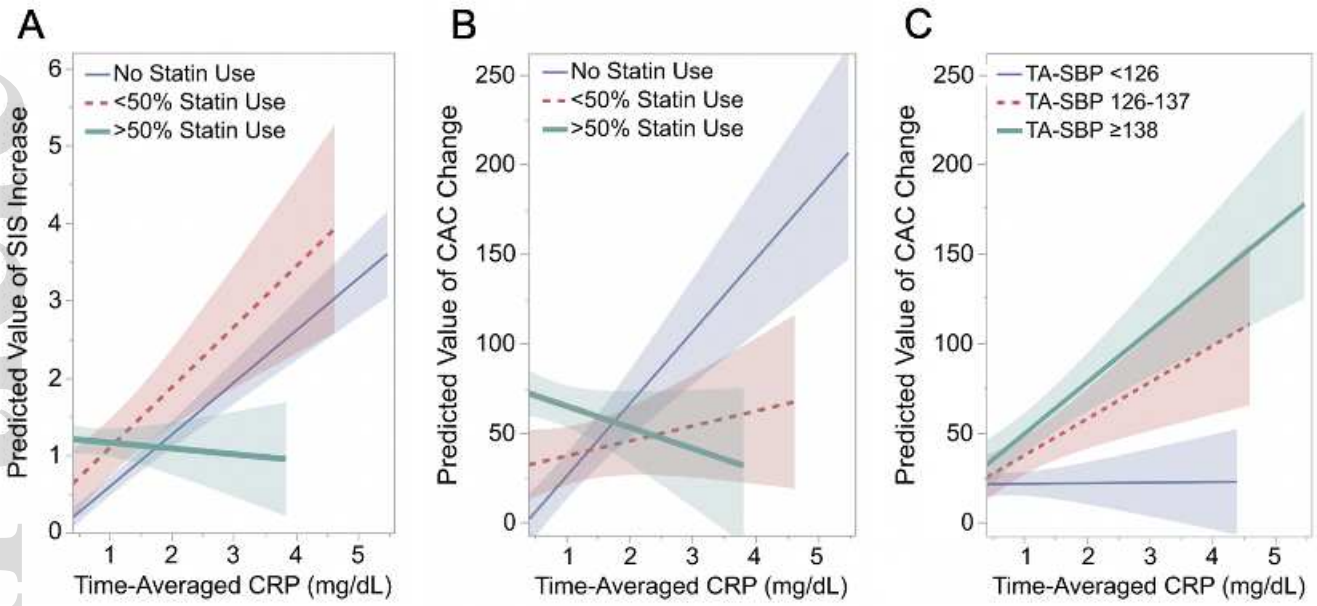
Table 3. Predictors of change in atherosclerosis burden by plaque type in RA

	Non-Calcified Plaque Progression		Mixed Plaque Progression		Calcified Plaque Progression	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age (years)		1.00 (0.93-1.07)		1.06 (1.00-1.12)*		1.18 (1.09-1.27)***
Sex (male)	1.17 (0.18-7.73)		1.34 (0.39-4.59)		1.78 (0.28-11.23)	
Hypertension	0.25 (0.03-2.11)		1.68 (0.56-5.02)		4.30 (1.55-11.96)**	3.53 (1.00-12.53)†
Dyslipidemia	0.40 (0.09-1.88)		0.50 (0.17-1.43)		1.49 (0.56-3.95)	
Diabetes	0.72 (0.07-7.18)		1.36 (0.36-5.17)		2.42 (0.81-7.27)	
Waist-to-height ratio	0.92 (0.82-1.04)		1.06 (0.99-1.13)		1.15 (1.08-1.22)***	1.16 (1.07-1.25)***
Time-averaged CRP (mg/dL)	1.09 (0.64-1.87)		0.70 (0.24-2.02)		3.12 (1.92-5.05)***	3.42 (1.85-6.35)***
Statin duration (years)	0.69 (0.55-0.88)**	0.72 (0.57-0.90)**	1.14 (0.94-1.39)		1.10 (0.93-1.31)	
bDMARD duration (years)	0.76 (0.60-0.96)*	0.77 (0.61-0.98)*	1.12 (0.93-1.34)		1.07 (0.92-1.25)	
Cumulative MTX (grams)	1.03 (0.99-1.08)		1.01 (0.98-1.04)		1.00 (0.97-1.03)	
Cumulative prednisone (grams)	0.99 (0.92-1.07)		1.05 (0.96-1.13)		1.08 (0.99-1.18)†	

OR: odds ratio, 95% CI: 95% confidence interval. $^{\dagger}p<0.1$, *p<0.05, **p<0.01, ***p<0.001. Model 1: adjusted for age and time in-between scans, Model 2: additional adjustments for all variables in the final multivariable model selected using backwards selection



art_41122_f1.tif



art_41122_f2.tiff