ARTHRITIS & RHEUMATOLOGY
Vol. 67, No. 7, July 2015, pp 1718–1728
DOI 10.1002/art.39114

Rosuvastatin-Induced Carotid Plaque Regression in Patients With Inflammatory Joint Diseases

The Rosuvastatin in Rheumatoid Arthritis, Ankylosing Spondylitis and Other Inflammatory Joint Diseases Study

S. Rollefstad,[1] E. Ikdahl,[1] J. Hisdal,[2] I. C. Olsen,[1] I. Holme,[3] H. B. Hammer,[1] K. T. Smerud,[4] G. D. Kitas,[5] T. R. Pedersen,[6] T. K. Kvien,[1] and A. G. Semb[1]

Objective. **Patients with rheumatoid arthritis (RA) and carotid artery plaques have an increased risk of acute coronary syndromes. Statin treatment with the goal of achieving a low-density lipoprotein (LDL) cholesterol level of ≤1.8 mmoles/liter (≤70 mg/dl) is recommended for individuals in the general population who have carotid plaques. The aim of the ROsuvastatin in Rheumatoid Arthritis, Ankylosing Spondylitis and other inflammatory joint diseases (RORA-AS) study was to evaluate the effect of 18 months of intensive lipid-lowering treatment with rosuvastatin with regard to change in carotid plaque height.**

Methods. **Eighty-six patients (60.5% of whom were female) with carotid plaques and inflammatory joint disease (55 with RA, 21 with AS, and 10 with psoriatic arthritis) were treated with rosuvastatin to obtain the LDL cholesterol goal. Carotid plaque height was evaluated by B-mode ultrasonography.**

Results. **The mean ± SD age of the patients was 60.8 ± 8.5 years, and the median compliance with rosuvastatin treatment was 97.9% (interquartile range [IQR] 96.0–99.4). At baseline, the median number and height of the carotid plaques were 1.0 (range 1–8) and 1.80 mm (IQR 1.60–2.10), respectively. The mean ± SD change in carotid plaque height after 18 months of treatment with rosuvastatin was −0.19 ± 0.35 mm ($P < 0.0001$). The mean ± SD baseline LDL cholesterol level was 4.0 ± 0.9 mmoles/liter (154.7 ± 34.8 mg/dl), and the mean reduction in the LDL cholesterol level was −2.3 mmoles/liter (95% confidence interval [95% CI] −2.48, −2.15) (−88.9 mg/dl [95% CI −95.9, −83.1]). The mean ± SD LDL cholesterol level during the 18 months of rosuvastatin treatment was 1.7 ± 0.4 mmoles/liter (area under the curve). After adjustment for age/sex/blood pressure, no linear relationship between a reduction in carotid plaque height and the level of LDL cholesterol exposure during the study period was observed. Attainment of the LDL cholesterol goal of ≤1.8 mmoles/liter (≤70 mg/dl) or the amount of change in the LDL cholesterol level during the study period did not influence the degree of carotid plaque height reduction.**

Conclusion. **Intensive lipid-lowering treatment with rosuvastatin induced atherosclerotic regression**

ClinicalTrials.gov identifier: NCT01389388. EudraCT database no. 2008-005551-20.

Supported by the South-Eastern Regional Health Authority of Norway. AstraZeneca provided the study drug.

[1]S. Rollefstad, MD, PhD, E. Ikdahl, MD, I. C. Olsen, PhD, H. B. Hammer, MD, PhD, T. K. Kvien, MD, A. G. Semb, MD, PhD: Diakonhjemmet Hospital, Oslo, Norway; [2]J. Hisdal, PhD: Oslo University Hospital, Aker, Oslo, Norway; [3]I. Holme, PhD: Oslo University Hospital, Ullevål, Oslo, Norway; [4]K. T. Smerud, MSc: Smerud Medical Research International AS, Oslo, Norway; [5]G. D. Kitas, MD, PhD, FRCP: The Dudley Group NHS Foundation Trust, West Midlands, UK; [6]T. R. Pedersen, MD, PhD: Centre of Preventive Medicine, Oslo University Hospital, Ullevål, and University of Oslo, Oslo, Norway.

Dr. Hammer has received consulting fees, speaking fees, and/or honoraria from Pfizer, Roche, AbbVie, UCB, and Merck Sharp & Dohme (less than $10,000 each). Dr. Pedersen has received speaking fees from Amgen (less than $10,000) and consulting/speaking fees from Merck Sharp & Dohme (more than $10,000). Dr. Semb has received speaking fees, consulting fees, and/or honoraria from Merck Sharp & Dohme, Schering Plough, AbbVie, Bristol-Myers Squibb, UCB, Wyeth/Pfizer, and Hoffmann-La Roche/Genentech (less than $10,000 each).

Address correspondence to S. Rollefstad, MD, PhD, Preventive Cardio-Rheuma Clinic, Department of Rheumatology, Diakonhjemmet Hospital, PO Box 23 Vinderen, NO-0319 Oslo, Norway. E-mail: s-rollef@diakonsyk.no or s.c.h.rollefstad@medisin.uio.no.

Submitted for publication October 20, 2014; accepted in revised form March 10, 2015.

and reduced the LDL cholesterol level significantly in patients with inflammatory joint disease.

The increased risk of cardiovascular (CV) disease in patients with rheumatoid arthritis (RA) has been known for decades (1). CV disease is a major factor in the widening mortality gap between patients with RA and the general population (2). Nevertheless, there is an "evidence vacuum" in the field of CV disease prevention and clinical outcome in patients with inflammatory joint disease, including RA, ankylosing spondylitis (AS), and psoriatic arthritis (PsA) (1). No specific CV prevention guidelines have been created for patients with inflammatory joint disease; thus, the current recommendations are to use the guidelines developed for the general population (3).

According to the recent European guidelines on CV disease prevention (4), the presence of carotid artery plaques is considered a strong CV risk factor. Patients with inflammatory joint disease have a high frequency of asymptomatic carotid plaques (5,6), which are easily visualized by ultrasonography of the carotid arteries. Furthermore, the presence of carotid plaques in patients with RA has been shown to predict future acute coronary syndromes (7). Strategies aimed at preventing CV disease, such as the initiation of statin treatment, are recommended for patients with carotid plaques (4). Reduced cholesterol levels achieved with statins was reported to induce regression of coronary atheroma volume and decrease the incidence of CV events in the general population (8). Statins have also been shown to significantly reduce the progression of carotid atherosclerosis (9). However, the effect of lipid-lowering treatment (when initiated on the basis of carotid plaques without previous CV events) has not yet been assessed in randomized trials.

A previous study in patients without inflammatory joint disease showed that despite achievement of very low levels of low-density lipoprotein (LDL) cholesterol, C-reactive protein (CRP) levels were associated with major acute coronary events after 2 years of intensive statin therapy (10). Considering the background inflammation experienced by patients with inflammatory joint disease, more evidence is needed regarding the effect of statins on atheroma regression in this group of patients with a high risk of CV events.

At the Preventive Cardio-Rheuma Clinic at Diakonhjemmet Hospital, Oslo, Norway, carotid ultrasonography is performed as part of the consultation in all patients with inflammatory joint disease who are referred for an evaluation of CV risk. When a carotid plaque is identified, statin treatment is initiated, with the goal of achieving an LDL cholesterol level of ≤1.8 mmoles/liter (≤70 mg/dl), according to guidelines (4).

In the ROsuvastatin in Rheumatoid Arthritis, Ankylosing Spondylitis and other inflammatory joint diseases (RORA-AS) study, the primary end point was change in carotid artery plaque size during 18 months of intensive lipid-lowering treatment with rosuvastatin. In the current study, changes in carotid plaque height were evaluated by ultrasonography, and we sought to determine whether biochemical and clinical variables were predictive of these changes.

PATIENTS AND METHODS

Patients and study design. The RORA-AS study was an open-label, prospective intervention study, which was performed during the time period January 2010 to August 2013. Patients with inflammatory joint disease were referred to the Preventive Cardio-Rheuma Clinic from the Department of Rheumatology at Diakonhjemmet Hospital, which has the responsibility for the treatment of patients with rheumatic joint diseases in Oslo, has regional functions in Southern and Eastern Norway, and has national responsibilities for complicated rehabilitation programs, and from primary care physicians. The criteria for referral to the Preventive Cardio-Rheuma Clinic were reported previously (11). Carotid plaque was identified according to previously described guidelines (6). Statin-naive patients of both sexes (ages 35–80 years) with RA, AS, or PsA who had ultrasound-verified asymptomatic carotid plaques with <50% stenosis were included in the study, after providing written informed consent.

The exclusion criteria were as follows: 1) contraindication for statin medication (hypersensitivity to statins, liver disease with transaminase levels of ≥2 times the upper limit of normal [ULN], previous statin-induced myopathy or severe hypersensitivity reactions to other statins, increased creatinine level, pregnancy or breastfeeding, fertile women not using contraceptives, cyclosporine treatment, treatment with medicinal products that have a known interaction with rosuvastatin, uncontrolled hypothyroidism defined as thyroid-stimulating hormone level of >1.5 times the ULN at the first visit [due to the connection between myopathy and hypothyroidism with statin treatment], creatinine clearance of <30 ml/minute, or an estimated glomerular filtration rate of <60 ml/minute); 2) secondary hyperlipidemia (primary hypothyroidism, nephrotic syndrome, creatinine level of >2 mg/dl, uncontrolled diabetes mellitus [glycated hemoglobin >10%], or plasma triglyceride level of >6.8 mmoles/liter [602.3 mg/dl]); and 3) other diseases or treatment that reduces the safety of rosuvastatin or treatment that would interfere with use of rosuvastatin and/or with the end points of the study (heart failure [New York Heart Association class IIIB/IV], gastrointestinal disease/treatment that may cause malabsorption of rosuvastatin, cancer, severe psychiatric disease, life-threatening ventricular arrhythmias, other medication that increases the risk of rhabdomyolysis, known alcohol abuse, or participation in other studies). The study was conducted in accordance with the Helsinki Declaration and was approved by the Regional Committee for Medical and Health Research Ethics (Region South East).

Overview of study visits. Patients who met the inclusion criteria were evaluated by a cardiologist at baseline and

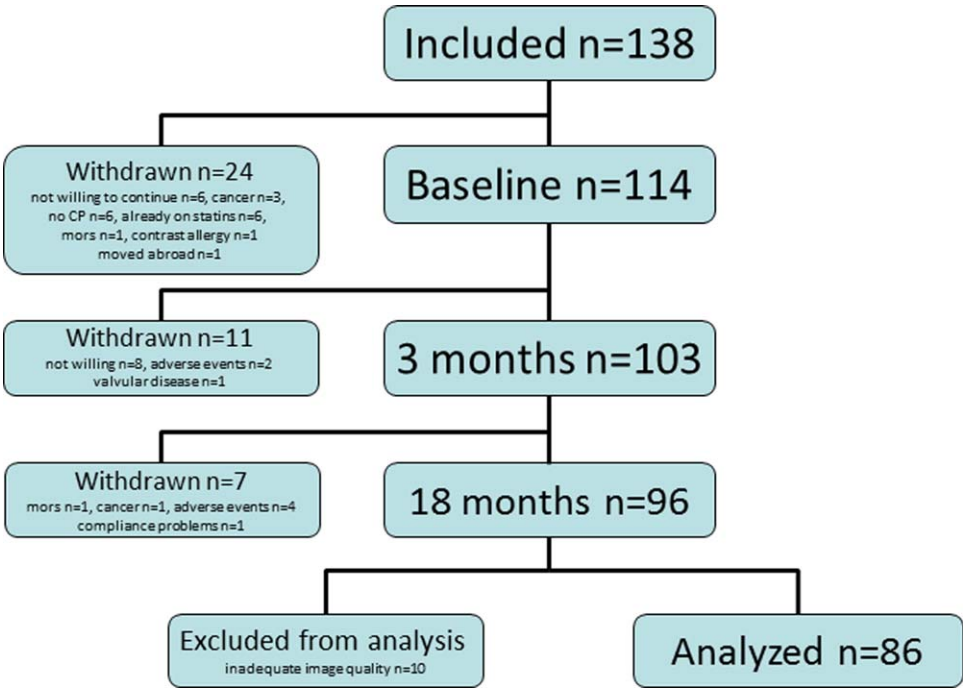

Figure 1. Flow chart of the ROsuvastatin in Rheumatoid Arthritis, Ankylosing Spondylitis and other inflammatory joint diseases (RORA-AS) study. Of the 138 patients who were initially included in the study, 24 patients withdrew. Ninety-six patients completed 18 months of treatment with rosuvastatin. Ultrasound images of the carotid arteries at baseline and after 18 months were deemed to be in the same dimensional plane in 86 patients and thereby were included in the main analysis. CP = carotid plaque. Color figure can be veiwed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.39114/abstract.

after 3 months and 18 months of treatment with rosuvastatin (provided by AstraZeneca). Joint disease activity was measured, and an evaluation for the risk of CV disease was performed, including laboratory testing and ultrasonography of the carotid arteries. The cardiologist was blinded with regard to the status of inflammatory joint disease activity. In addition, less-comprehensive assessments including laboratory testing and recording of adverse events were conducted (at weeks 2, 4, and 6 after baseline) if the LDL cholesterol goal was not reached and up-titration of the rosuvastatin dose was indicated.

CV risk evaluation. CV risk factors, including smoking status, diabetes, medication history, history of premature CV disease in first-degree relatives (male relatives younger than age 55 years/female relatives younger than age 65 years), and the presence of established CV disease were recorded. The levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, liver enzymes, creatine kinase (CK), and CRP were measured by routine procedures at the Diakonhjemmet Hospital laboratory (European Standard accredited 2009) using a Cobas 600 analyzer (12). The erythrocyte sedimentation rate (ESR) was analyzed using the Westergren method, and the concentration of LDL cholesterol was calculated using the method described by Friedewald et al (13). Blood pressure (BP) was measured after 5 minutes of resting in a supine position, using an Omron M7 apparatus. If BP exceeded 140/90 mm Hg, the mean of 3 consecutive measurements was calculated. A 12-lead electrocardiogram was recorded digitally. Further details concerning CV risk evaluation at the Preventive Cardio-Rheuma Clinic have been reported previously (11,14).

Carotid ultrasonography. Bilateral B-mode ultrasound examinations of the carotid arteries were performed by an experienced sonographer using a 12-MHz linear matrix array transducer (GE Vivid-7 ultrasound scanner; GE Vingmed Ultrasound). The readers were blinded with regard to disease activity and the CV disease risk profile. Intima-media thickness (IMT) measurements were performed bilaterally in the far wall of the common carotid artery over a 5-mm–long segment, from ~10 mm proximal to the start of the carotid bulb. To ensure that the longitudinal ultrasound images at baseline and after 18 months of rosuvastatin treatment were in the same dimensional plane, several steps were performed: 1) ensure that both the near wall and the far wall of the artery were visualized with sharp edges, indicating isonation of ~90° to the vessel wall to avoid overestimation of IMT and plaque height, and 2) use images from the baseline assessment as a reference at the 18-month visit, to optimize equality of the dimensional plane at both time points. The IMT and plaque height measurements were read offline by an experienced vascular physiologist (JH) and a cardiologist (AGS), as previously described (15).

Atherosclerotic plaques were identified bilaterally in the longitudinal view as protrusions into the lumen of ≥1.5 mm or at least 2 times the adjacent IMT. Carotid plaque height was measured from the leading edge at the maximum height of the plaque to the leading edge of the adventitia, in the longitudinal view. The presence of a plaque was verified by a cross-sectional

Table 1. Baseline characteristics of the patients with inflammatory joint disease*

Characteristic	All (n = 86)	RA (n = 55)	AS (n = 21)	PsA (n = 10)
Age, years	60.8 ± 8.5	62.2 ± 8.6	58.8 ± 8.3	57.2 ± 7.6
Men/women, no. (%)†	34 (39.5)/52 (60.5)	15 (27.3)/40 (72.7)	14 (66.7)/7 (33.3)	5 (50.0)/5 (50.0)
Disease duration, median (IQR) years	16.0 (8.0–25.0)	16.0 (7.0–22.3)	21.0 (9.5–28.0)	11.5 (1.5–29.5)
CV risk factors				
Smoking, no. (%)	16 (18.6)	11 (20.0)	3 (14.3)	2 (20.0)
BMI, kg/m^2	25.3 ± 3.2	25.0 ± 3.3	25.4 ± 2.6	26.4 ± 3.7
Total cholesterol, mmoles/liter (mg/dl)	6.43 ± 1.09 (248.65 ± 42.15)	6.44 ± 1.16 (249.03 ± 44.86)	6.34 ± 0.90 (245.17 ± 34.80)	6.55 ± 1.10 (253.29 ± 42.54)
HDL cholesterol, mmoles/liter (mg/dl)	1.72 ± 0.53 (66.51 ± 20.49)	1.82 ± 0.53 (70.38 ± 20.49)	1.52 ± 0.46 (58.78 ± 17.79)	1.63 ± 0.53 (63.03 ± 20.49)
Triglycerides, median (IQR) mmoles/liter (mg/dl)	1.2 (0.9–1.8) (106.3 [79.7–159.4])	1.1 (0.9–1.6) (97.4 [79.7–141.7])	1.6 (1.1–2.1) (141.7 [97.4–177.2])	1.1 (0.7–2.9) (97.4 [62.0–256.9])
LDL cholesterol, mmoles/liter (mg/dl)	4.05 ± 1.00 (156.61 ± 38.67)	4.01 ± 1.05 (155.07 ± 40.60)	4.08 ± 0.90 (157.77 ± 34.80)	4.23 ± 1.01 (163.57 ± 39.06)
Systolic BP, mm Hg	144.2 ± 19.3	143.7 ± 20.4	145.1 ± 13.0	145.4 ± 25.0
Diastolic BP, mm Hg	84.1 ± 9.3	83.4 ± 9.3	84.6 ± 8.7	86.9 ± 10.8
Comorbidities				
Hypertension, no. (%)	51 (59.3)	32 (58.2)	14 (66.7)	5 (50.0)
Diabetes mellitus, no. (%)	6 (7.0)	4 (7.3)	2 (9.5)	0 (0.0)
CV disease, no. (%)	9 (10.5)	6 (10.9)	3 (14.3)	0 (0.0)
Carotid artery plaques, median (range)	1 (1–5)	1 (1–5)	1 (1–3)	2 (1–3)
Biomarkers				
ESR, mm/hour	14.4 ± 9.3	15.3 ± 9.6	12.1 ± 9.8	13.9 ± 6.0
CRP, median (IQR) mg/liter	2.0 (1.0–4.0)	3.0 (1.0–4.0)	1.0 (1.0–5.0)	2.5 (1.8–6.5)
AST, units/liter	28.6 ± 10.4	28.5 ± 11.0	29.0 ± 9.6	28.5 ± 9.4
ALT, units/liter	30.6 ± 20.5	28.2 ± 19.3	34.4 ± 22.8	35.9 ± 21.7
Creatine kinase, units/liter	89.7 ± 61.3	86.8 ± 68.9	101.2 ± 48.8	75.6 ± 31.4
Medication, no. (%)				
Prednisolone	23 (26.7)	19 (34.5)	2 (9.5)	2 (20.0)
NSAIDs	37 (43.0)	22 (40.0)	11 (52.4)	4 (40.0)
Synthetic DMARDs	49 (57.0)	34 (61.8)	6 (28.6)	9 (90.0)†
Biologic DMARDs	27 (34.2)	16 (32.0)	6 (31.6)	5 (50.0)
No DMARDs	23 (26.7)	13 (23.6)	9 (42.9)	1 (10.0)
Antihypertensive agents	23 (26.7)	17 (30.9)	4 (19.0)	2 (20.0)

* Except where indicated otherwise, values are the mean ± SD. IQR = interquartile range; CV = cardiovascular; BMI = body mass index; HDL = high-density lipoprotein; LDL = low-density lipoprotein; BP = blood pressure; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; AST = aspartate aminotransferase; ALT = alanine aminotransferase; NSAIDs = nonsteroidal antiinflammatory drugs; DMARDs = disease-modifying antirheumatic drugs.

† $P = 0.01$, overall comparison of variables between the rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) groups, by analysis of variance.

image. Plaque height was analyzed only if a sharp delineation of the plaque was obtained and the images from baseline and 18 months were deemed to be in the same dimensional plane. An intraclass correlation coefficient (ICC) for the IMT values obtained in our laboratory was previously reported to be 0.985 (95% confidence interval [95% CI] 0.975, 0.991) (15). The correlation of the carotid plaque height measurements between the 2 readers was good, with an ICC of 0.991 (95% CI 0.981, 0.996). Information regarding interrater and intrarater reliability is available from the corresponding author.

Study medication. Patients started treatment with rosuvastatin at a dosage of 20 mg/day, except for patients ages >70 years, who received an initial dosage of 5 mg/day. The starting dose was titrated up by doubling the dose if an LDL cholesterol level of 1.6–1.8 mmoles/liter (62–70 mg/dl) was not achieved (for patients ≤70 years), or by doubling the dose every 14 days for patients >70 years until the LDL cholesterol goal was obtained or a maximal dosage of 40 mg/day was reached. The patients continued to receive rosuvastatin treatment for a total of 18 months. The patients were given the necessary number of rosuvastatin tablets at each visit. At the following visits, surplus medication was returned to the investigator. Compliance was calculated as a percentage, based on the number of tablets returned.

Measures of disease activity. A trained study nurse who was blinded with regard to the CV risk profile of the patients assessed the number of swollen and tender joints. Disease activity in patients with RA was assessed by the Disease Activity Score in 28 joints (DAS28) (16). Digital conventional radiographs of the hands and feet were obtained for the patients with RA and were scored according to the Sharp/van der Heijde method (17), in order to address bone damage possibly caused by accumulated disease activity. Disease activity in the patients with AS was measured using the Ankylosing Spondylitis Disease Activity Score (ASDAS) (18).

Statistical analysis. Descriptive statistics are expressed as the number (%) for dichotomized variables and the mean ± SD and median (interquartile range [IQR]) for normally and non-normally distributed characteristics,

Table 2. Changes in carotid plaque height and intima-media thickness in patients receiving biologic DMARDs, patients receiving synthetic DMARDs, and patients receiving no DMARDs*

	Baseline	18 months	Change	P†
Carotid plaque height				
All patients	1.92 ± 0.52	1.72 ± 0.48	−0.19 ± 0.35 (−0.27, −0.12)	<0.0001
Biologic DMARDs	1.89 ± 0.58	1.80 ± 0.54	−0.09 ± 0.37 (−0.22, 0.04)	0.15
Synthetic DMARD monotherapy	1.93 ± 0.50	1.67 ± 0.46	−0.26 ± 0.29 (0.14, 0.37)	<0.0001
No DMARDs	1.97 ± 0.62	1.73 ± 0.52	−0.24 ± 0.35 (0.12, 0.37)	<0.0001
Difference‡				
Biologic vs. synthetic DMARDs	–	–	−0.23 ± 0.09 (−0.40, −0.05)	0.01
Biologic DMARDs vs. no DMARDs	–	–	0.21 ± 0.10 (0.01, 0.40)	0.04
Synthetic DMARDs vs. no DMARDs	–	–	0.01 ± 0.09 (−0.17, 0.18)	0.93
Intima-media thickness				
All patients	0.73 ± 0.15	0.71 ± 0.14	−0.01 ± 0.08 (−0.03, 0.01)	0.14
Biologic DMARDs	0.70 ± 0.16	0.71 ± 0.16	0.01 ± 0.07 (−0.01, 0.03)	0.40
Synthetic DMARD monotherapy	0.72 ± 0.15	0.69 ± 0.12	0.03 ± 0.10 (−0.01, 0.07)	0.10
No DMARDs	0.73 ± 0.15	0.71 ± 0.14	0.01 ± 0.08 (−0.005, 0.03)	0.14
Difference‡				
Biologic vs. synthetic DMARDs	–	–	−0.04 ± 0.02 (−0.09, 0.01)	0.08
Biologic DMARDs vs. no DMARDs	–	–	0.03 ± 0.02 (−0.02, 0.07)	0.22
Synthetic DMARDs vs. no DMARDs	–	–	0.03 ± 0.02 (−0.02, 0.08)	0.26

* Except where indicated otherwise, values are the mean ± SD mm (95% confidence interval). DMARDs = disease-modifying antirheumatic drugs.
† The paired-sample *t*-test was used for all analyses except the analyses for differences between groups, which were performed by *t*-test for independent samples.
‡ Values are the mean ± SEM mm (95% confidence interval).

respectively. The *t*-test for independent samples, analysis of variance, and the chi-square test were used to compare variables across groups, as appropriate. Non-normally distributed variables were log-transformed before the analyses were conducted. The numbers of carotid plaques across the various inflammatory joint disease diagnoses was compared using the nonparametric Kruskal-Wallis test. The paired-sample *t*-test was applied when comparing continuous variables at baseline and after 18 months.

Weighted variables for LDL cholesterol, the CRP, the ESR, and the DAS28 were computed, taking the period of time between visits into consideration (area under the curve). Thus, the levels of these variables during the study period in relation to changes in carotid plaque height after 18 months of intensive lipid-lowering treatment with rosuvastatin could be evaluated.

A linear regression analysis was performed using change in carotid plaque height as the dependent variable; the independent variables were age, sex, weighted DAS28, and use of biologic disease-modifying antirheumatic drugs (DMARDs). The residuals were normally distributed.

A logistic regression model was constructed, with reduction versus increase in carotid plaque height as the dependent variable, in order to assess the independent contribution of biomarkers of inflammation, use of antirheumatic drugs, and presence of CV risk factors such as cholesterol levels and BP. We chose a conservative approach in which the dependent variable in that progression was defined as either stabilization or an increase in carotid plaque height, while regression was defined solely as a reduction in carotid plaque height at the end of the study period. The goodness of fit of the model was assessed by calibration plots.

To evaluate the impact of several baseline factors (carotid plaque height, treatment with biologic DMARDs, biomarkers of inflammation [CRP and ESR], sex, and age) on the change in carotid plaque height after 18 months of rosuvastatin treatment, we used mixed models to account for possible dependency between multiple carotid plaques in the same patient. Thus, when applying mixed models, the analysis was performed at the carotid plaque level, which is in contrast to all previously described analyses, which were performed at the patient level. The analyses were performed using IBM SPSS version 21.

RESULTS

Descriptive data. A flow chart of the RORA-AS study is shown in Figure 1. Apart from expected sex differences ($P = 0.01$) and use of synthetic DMARDs ($P = 0.01$), the baseline characteristics of the subgroups of patients with RA, AS, and PsA were very similar (Table 1). At baseline, 11 patients (12.8%) had a total cholesterol level of >7 mmoles/liter (>271 mg/dl) and an LDL cholesterol level of >5 mmoles/liter (>193 mg/dl). Information regarding the distribution of total cholesterol and LDL cholesterol levels among the patients is available from the corresponding author.

The median compliance (calculated as a percentage, based on the number of tablets returned) with rosuvastatin treatment was 97.9% (IQR 96.0–99.4). At baseline, the median number of carotid plaques was 1.0 (range 1–8), with a median height of 1.80 mm (IQR 1.60–2.10). After 18 months of treatment with rosuvastatin (mean ± SD dose 30.7 ± 14.7 mg), the mean ± SD change in carotid plaque height was −0.19 ± 0.35 mm ($P < 0.0001$). There was no significant change in IMT between baseline and the end of the study period ($P = 0.14$) (Table 2). Forty-six patients (53.5%) had

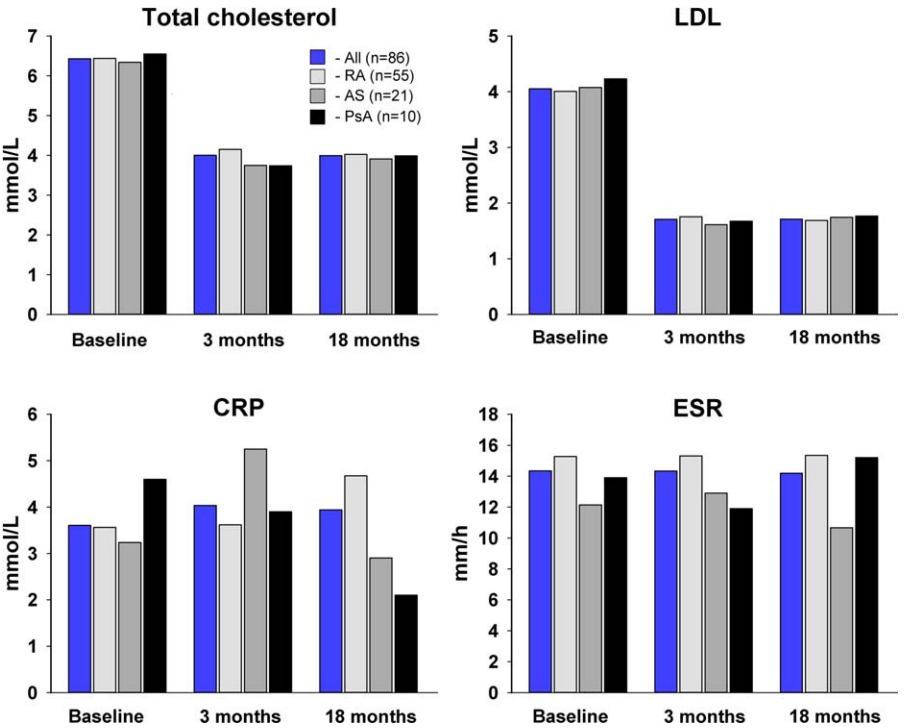

Figure 2. Changes in the total cholesterol level, the low-density lipoprotein (LDL) cholesterol level, the C-reactive protein (CRP) level, and the erythrocyte sedimentation rate (ESR) during the study period. The mean ± SD LDL cholesterol level at baseline was 4.0 ± 0.9 mmoles/liter (154.7 ± 34.8 mg/dl), and the mean reduction in the LDL cholesterol level at 18 months was −2.3 mmoles/liter (95% confidence interval [95% CI) −2.48, −2.15) (−88.9 mg/dl [95% CI −95.90, −83.14]) ($P < 0.001$). The mean level of LDL cholesterol exposure during the 18 months of rosuvastatin treatment (the weighted variable) was 1.7 ± 0.4 mmoles/liter (area under the curve). Fifty-three patients (61.6%) achieved the LDL cholesterol goal of ≤1.8 mmoles/liter (≤70 mg/dl), and there was also a significant reduction in the total cholesterol level after 3 months and 18 months of rosuvastatin treatment ($P < 0.001$). The same pattern was not observed for the biomarkers of inflammation (for the CRP level, $P = 0.50$ and $P = 0.69$, respectively; for the ESR, $P = 0.76$ and $P = 0.89$, respectively). RA = rheumatoid arthritis; AS = ankylosing spondylitis; PsA = psoriatic arthritis.

multiple carotid plaques (additional information is available from the corresponding author). In 72% of the patients with multiple carotid plaques, a reduction in carotid plaque height was seen in more than half of the plaques (additional information is available from the corresponding author).

Changes in lipid levels and biomarkers of inflammation during the study period are shown in Figure 2. Fifty-three patients (61.6%) achieved the LDL cholesterol goal of ≤1.8 mmoles/liter (≤70 mg/dl) during the study period (area under the curve). Nine patients (10.5%) were older than age 70 years when they were included in the study, and these patients received a significantly lower dose of rosuvastatin compared with those ages ≤70 years (mean ± SD 19.4 ± 16.1 mg versus 30.9 ± 11.8 mg; $P = 0.01$). However, there was no difference between these 2 groups regarding achievement of the LDL cholesterol goal of 1.8 mmoles/liter (70 mg/dl) (61.0% of patients ages ≤70 years and 66.7% of those older than age 70 years; $P = 0.74$). The mean ± SD change in the LDL cholesterol level between the first consultation and the final consultation was −55.8 ± 8.7%. Sixty-four patients (74.4%) achieved a reduction in the LDL cholesterol level of ≥50%. No change in the DAS28 ($P = 0.15$) or ASDAS ($P = 0.40$) was observed during the study period (data not shown). Information regarding adverse events is available from the corresponding author.

Associations with change in carotid plaque height. The change in carotid plaque height in relation to the LDL cholesterol level is shown in Figures 3A–C. Attainment of an LDL cholesterol level of ≤1.8 mmoles/liter (≤70 mg/dl) during 18 months of rosuvastatin treatment was not associated with the degree of carotid plaque height reduction ($P = 0.46$). The lack of a relationship between the degree of carotid plaque height reduction and the level of LDL cholesterol, the percent change in LDL cholesterol, change in the LDL cholesterol level, or attainment of the LDL cholesterol goal for patients with inflammatory joint disease was consistent in separate analyses for RA, AS, and PsA (data not shown).

The 86 patients had a total of 161 carotid plaques that were included in the analyses. There was a significant

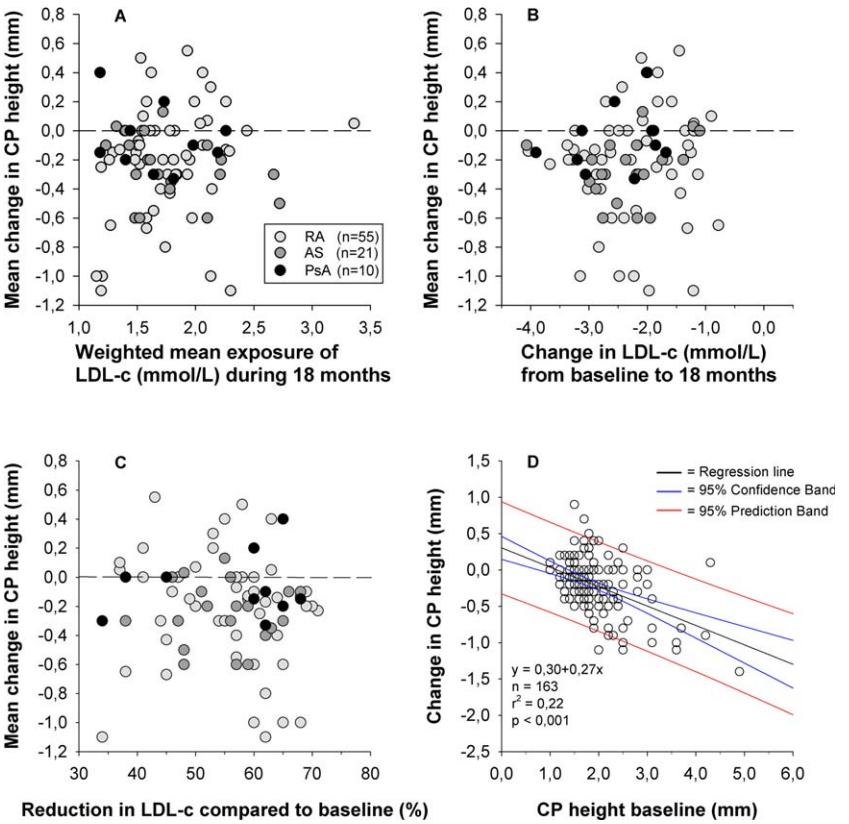

Figure 3. Changes in carotid plaque (CP) height in relation to the low-density lipoprotein cholesterol (LDL-c) level. **A–C,** Results of a linear regression analysis (adjusted for age and sex and blood pressure) showing no relationship between the change in carotid plaque height and the weighted mean exposure to LDL cholesterol during the study period (**A**), the change in the LDL cholesterol level from baseline to 18 months (**B**), and the percent reduction in the LDL cholesterol level compared with baseline (**C**). **D,** Significant linear relationship between the baseline carotid plaque height and the reduction in plaque height after 18 months of treatment with rosuvastatin. RA = rheumatoid arthritis; AS = ankylosing spondylitis; PsA = psoriatic arthritis. Color figure can be veiwed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.39114/abstract.

linear relationship between baseline carotid plaque height and reduction in plaque height ($P < 0.001$), in which the highest plaques at baseline had the greatest height reduction after 18 months of treatment with rosuvastatin (Figure 3D). Furthermore, age had a significant impact on plaque height reduction ($P = 0.01$), with the youngest patients having the greatest reduction in plaque height. Representative ultrasound images of the carotid artery with a carotid plaque, at baseline and after 18 months of treatment, are shown in Figure 4.

In a logistic regression model, age, sex, BP, and biomarkers of inflammation did not contribute to a reduction in carotid plaque height. Patients receiving biologic DMARDs did not achieve a reduction in carotid plaque height and hence differed significantly from both patients receiving synthetic DMARDs as monotherapy ($P = 0.01$) and those not receiving DMARDs ($P = 0.04$). There was a significant reduction in carotid plaque height during the study period in both patients receiving synthetic DMARDs as monotherapy and those not receiving DMARDs (both $P < 0.0001$) (Table 2). In the linear regression analysis, treatment with synthetic DMARDs as monotherapy was not significantly associated with either the dichotomous dependent variable regression versus progression of carotid plaque height ($P = 0.80$), or with the continuous dependent variable change in carotid plaque height during the study period ($P = 0.45$).

Disease activity during the study period as measured by the DAS28 (area under the curve) was inversely associated with change in carotid plaque height ($P = 0.02$); patients with the highest level of disease activity had the smallest change in carotid plaque height and vice versa. Demographic data, the presence of CV risk factors/comorbidities, disease activity, joint damage as measured by the Sharp/van der Heijde method, laboratory values, and medication use at baseline were comparable for patients not receiving biologic DMARDs and those receiving biologic DMARDs (additional information is available

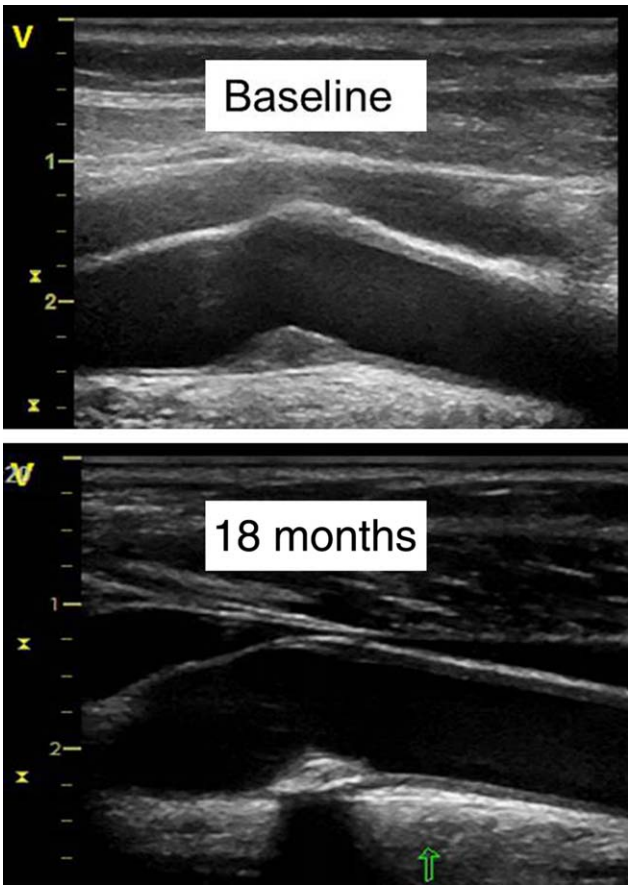

Figure 4. Change in carotid plaque height from baseline to 18 months. Representative ultrasound images show an atherosclerotic plaque in the far wall of the bulb of the right carotid artery. At baseline, the plaque has a low density. After 18 months of rosuvastatin treatment, the height of the plaque is reduced and the density is increased, and calcification of the plaque has occurred (with acoustic shadowing below), reflecting stabilization of the plaque. Color figure can be veiwed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.39114/abstract.

from the corresponding author), except that the prevalence of documented CV disease was significantly higher in patients not receiving biologic DMARDs ($P = 0.02$).

In the logistic regression analysis, the change in carotid plaque height was not related to changes in body mass index ($P = 0.50$), smoking status ($P = 0.48$), or treatment with antirheumatic medication (for synthetic DMARDs, $P = 0.59$; for biologic DMARDs, $P = 0.08$) during the study period.

DISCUSSION

This study is the first to show that preventive treatment of CV disease with a statin reduced atherosclerosis in patients with inflammatory joint disease. We make this claim even in the absence of a placebo control arm, because we assume that untreated patients with inflammatory joint disease will not spontaneously achieve regression of the atherosclerotic process. The results of the RORA-AS study revealed that treatment with rosuvastatin for 18 months induced regression of carotid plaque height and reduced the LDL cholesterol level significantly in patients with inflammatory joint disease. The degree of carotid plaque height reduction was inversely related to the accumulated disease activity during the study period (the weighted DAS28) but was not influenced by attainment of the LDL cholesterol goal, the degree of change in the LDL cholesterol level, the percent change in the LDL cholesterol level, or LDL cholesterol exposure.

Intensive lipid-lowering treatment with both rosuvastatin and atorvastatin has been shown to reduce the coronary atheroma volume in patients without inflammatory joint disease (8). Despite a lower level of LDL cholesterol and a higher level of HDL cholesterol in the patients treated with rosuvastatin, the same degree of atheroma volume regression was seen in the rosuvastatin group and the atorvastatin group, indicating that atheroma regression can be obtained with high-dose statin treatment and low levels of LDL cholesterol ($\leq$1.8 mmoles/liter or $\leq$70 mg/dl). Aggressive lipid-lowering treatment has been shown to be more effective than moderate lipid-lowering treatment for carotid plaque stabilization in patients with carotid stenosis (19). The lack of association between change in carotid plaque height and achievement of the LDL cholesterol goal in the RORA-AS study suggests that it may be high-dose statin treatment that induces atheroma regression in patients with inflammatory joint disease rather than achievement of the recommended LDL cholesterol goal (4). Whether a low LDL cholesterol level in combination with intensive statin therapy is necessary to obtain carotid plaque regression in patients with inflammatory joint disease cannot be concluded based on our results, because we were not able to detect a linear relationship between LDL cholesterol levels and the degree of reduction in carotid plaque height.

From another perspective, it has been shown that treatment with statins induced a reduction in the CRP level along with a >40% reduction in the hazard ratio concerning the rates of a first major CV event in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study (20). Disease activity as measured by the DAS28 comprises systemic inflammation as well as joint inflammation. Thus, the impact of disease activity on the carotid plaque height reduction in rosuvastatin-treated patients with inflammatory joint disease is consistent with results from the JUPITER trial, because disease activity is a

composite measure that includes biomarkers of inflammation. In fact, high disease activity has been reported to influence surrogate CV end points such as carotid plaque vulnerability (15) in addition to being associated with increased vascular stiffness (21) and abnormal left ventricular geometry (22). Lowering disease activity in patients with RA may thus be of importance to alleviate the risk of CV disease.

Intensive statin treatment is associated with lower rates of clinical CV events in large randomized trials in patients without inflammatory joint disease (23). Prospective, randomized, placebo-controlled trials of statin in patients with inflammatory joint disease are lacking; however, promising results from post hoc analyses of 2 large statin trials (the Incremental Decrease in End Points Through Aggressive Lipid Lowering study [24] and the Treating to New Targets study [25]) showed that patients with and those without inflammatory joint disease experienced comparable cardioprotection from statin treatment, although the confidence intervals were somewhat wide (26). In addition, intensive statin treatment has been shown to attenuate the progression of coronary artery plaques (27). Other investigators have noted the possibility of a variable influence of clinical and biochemical factors on atherosclerotic plaques in response to intensive statin treatment. Puri et al recently reported that greater baseline coronary artery plaque volume was consistently related to more atheroma regression with intensive versus moderate statin treatment (10), which is consistent with the results of our study in patients with inflammatory joint disease, where the highest carotid plaques at baseline had the greatest height reduction after 18 months.

There are conflicting results regarding the impact of biologic DMARD treatment on the risk of CV disease. Adverse effects of biologic DMARDs on lipids have been reported previously (28,29). However, a systematic literature review suggests that tumor necrosis factor (TNF) inhibitors may reduce the risk of CV disease in patients with RA, but that the reduction in CV disease is not as consistent as that reported for methotrexate (MTX) treatment (30,31). In studies evaluating the influence of biologic DMARDs on CV events, a lack of information regarding whether antirheumatic medication consisted of monotherapy with a TNF inhibitor or combination therapy with MTX is a recurrent problem. The concurrent use of MTX is therefore a potential confounder. In contrast, Greenberg et al did not observe a cardioprotective effect of MTX (32), and hence the influence of antirheumatic medication on CV end points should be further investigated. Moreover, the published studies on this topic have short follow-up times, while the progression of atherosclerosis is a protracted process. Finally, few studies are adjusted for confounding by indication, which is a major concern in that patients with the most severe and longstanding rheumatic disease are more likely to be treated with biologic DMARDs. Interestingly, it was recently reported that patients with PsA treated with TNF inhibitors had an increase in IMT that was 4 times greater than the expected age-related increase (33). In the RORA-AS study, we demonstrated a significant difference in carotid plaque height reduction between patients receiving biologic DMARDs and those not receiving biologic DMARDs, in favor of those not receiving biologic DMARDs.

The RORA-AS study has limitations. It was conducted without a control group receiving placebo, because it was considered unethical to deviate from guideline-recommended statin treatment in patients with established atherosclerosis. It is well known, however, that atherosclerosis increases over time, and placebo-treated patients would most likely not achieve spontaneous regression of an atherosclerotic plaque. Thus, comparing a placebo group with a statin-treated group would probably result in a larger difference in the primary end point compared with the results of our study, in which the statin-treated patients acted as their own controls. Furthermore, the primary end point is a surrogate marker of CV disease. Nevertheless, the presence of carotid plaques increases the risk of acute coronary syndrome 2.5-fold in patients with RA compared with RA patients without carotid plaques (7).

Future studies are needed to reveal whether the lack of association between change in carotid plaque height and exposure to LDL cholesterol, degree of change in LDL cholesterol, or LDL cholesterol goal attainment in our study is attributable to specific factors in patients with inflammatory joint disease that differ from those in the general population (e.g., systemic inflammation, use of immunosuppressive medication) or is a consequence of a Type II error caused by lack of power.

Another limitation can be related to biologic medication, which may have caused confounding by indication for inclusion in the study. However, baseline characteristics, and especially disease activity as measured by the DAS28 and degree of joint damage (Sharp/van der Heijde score), were comparable in patients receiving biologic DMARDs and those not receiving biologic DMARDS.

Finally, ultrasound is a 2-dimensional image modality and therefore has limitations. "Atherosclerosis regression" trials of lipid-modifying pharmacotherapy have established that IMT of the carotid arteries, as measured by B-mode ultrasound, is a valued surrogate marker of the progression of atherosclerotic disease (34). Atherosclerotic plaques are a further development in what is defined as a thickened intima-media, and the changes seen in trials in which change in IMT has been used as the end point are

smaller (for example in the ASAP study where the difference between the 2 groups was 0.06 mm [35]) compared with the change in carotid plaque height seen in our study (−0.19 mm), supporting the validity of detecting plaque regression by using B-mode ultrasound. Although we are fully aware that other imaging methods (magnetic resonance imaging or optical coherence tomography) more accurately measure changes in carotid plaques, the advantage of ultrasound examination is that it is inexpensive, does not expose the patient to radiation, and is not time consuming.

The maximum height of the carotid plaques was measured in the longitudinal view, because of the challenge of determining the baseline of the plaque in cross-sectional images due to the Glagovian phenomenon (36) and, often, acoustic shadowing below the plaque. Several techniques for carotid plaque quantification are in use, including measures of maximum height, area, and volume. In our longitudinal study, it was challenging to determine the transition between the edges of a plaque and the surrounding IMT in repetitive measurements, and thus, the measures of plaque area were considered unreliable. However, measurements of maximum plaque height, plaque area, and plaque volumes have been used in previous studies in the general population (37). Interestingly, the presence of carotid plaques as verified by any of these techniques (including measures of maximum carotid plaque height) has repeatedly been shown to be associated with CV events (38). The gray-scale median (GSM) technique uses image normalization and digital standardization of the plaque morphology. In the RORA-AS study, we observed that image normalization and digital standardization from baseline to followup after 18 months of rosuvastatin treatment had low reproducibility. Therefore, a limitation of our study is that we could not apply the GSM technique for evaluation of plaque morphology. However, the impact of plaque characteristics on predicting CV disease outcomes is not well established (39).

We conclude that intensive lipid-lowering treatment with rosuvastatin induced atherosclerosis regression, as evaluated by the change in carotid plaque height, in patients with inflammatory joint disease. Our results also indicate that disease activity may influence the effect of anti-atherosclerosis treatment. Prospective randomized studies of statins are warranted to reveal whether height reduction in asymptomatic carotid plaques will have an impact on future CV events.

ACKNOWLEDGMENTS

We thank Anne S. Eirheim for conducting the carotid ultrasound procedure, Anne-Kari Brun for organizing the study visits and for performing the tender/swollen joint counts, Cecilie Okkenhaug for performing the laboratory procedures, and Pernille Bøyesen for scoring the radiographs.

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. Rollefstad had full access to all of 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. Hisdal, Kitas, Kvien, Semb.

Acquisition of data. Rollefstad, Ikdahl, Hisdal, Holme, Hammer, Semb.

Analysis and interpretation of data. Rollefstad, Ikdahl, Hisdal, Olsen, Holme, Smerud, Kitas, Pedersen, Kvien, Semb.

REFERENCES

1. Semb AG, Rollefstad S, van Riel P, Kitas GD, Matteson EL, Gabriel SE. Cardiovascular disease assessment in rheumatoid arthritis: a guide to translating knowledge of cardiovascular risk into clinical practice. Ann Rheum Dis 2014;73:1284–8.
2. Gonzalez A, Maradit KH, Crowson CS, Nicola PJ, Davis JM III, Therneau TM, et al. The widening mortality gap between rheumatoid arthritis patients and the general population. Arthritis Rheum 2007;56:3583–7.
3. Solomon DH, Peters MJ, Nurmohamed MT, Dixon W. Motion for debate: the data support evidence-based management recommendations for cardiovascular disease in rheumatoid arthritis. Arthritis Rheum 2013;65:1675–83.
4. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WM, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Atherosclerosis 2012;223:1–68.
5. Stamatelopoulos KS, Kitas GD, Papamichael CM, Chryssohoou E, Kyrkou K, Georgiopoulos G, et al. Atherosclerosis in rheumatoid arthritis versus diabetes: a comparative study. Arterioscler Thromb Vasc Biol 2009;29:1702–8.
6. Roman MJ, Moeller E, Davis A, Paget SA, Crow MK, Lockshin MD, et al. Preclinical carotid atherosclerosis in patients with rheumatoid arthritis. Ann Intern Med 2006;144:249–56.
7. Evans MR, Escalante A, Battafarano DF, Freeman GL, O'Leary DH, del Rincon I. Carotid atherosclerosis predicts incident acute coronary syndromes in rheumatoid arthritis. Arthritis Rheum 2011;63:1211–20.
8. 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.
9. Kang S, Wu Y, Li X. Effects of statin therapy on the progression of carotid atherosclerosis: a systematic review and meta-analysis. Atherosclerosis 2004;177:433–42.
10. Puri R, Nissen SE, Shao M, Ballantyne CM, Barter PJ, Chapman MJ, et al. Coronary atheroma volume and cardiovascular events during maximally intensive statin therapy. Eur Heart J 2013;34:3182–90.
11. Rollefstad S, Kvien TK, Holme I, Eirheim AS, Pedersen TR, Semb AG. Treatment to lipid targets in patients with inflammatory joint diseases in a preventive cardio-rheuma clinic. Ann Rheum Dis 2013;72:1968–74.
12. Van Gammeren AJ, van Gool N, de Groot MJ, Cobbaert CM. Analytical performance evaluation of the Cobas 6000 analyzer: special emphasis on trueness verification. Clin Chem Lab Med 2008;46:863–71.

13. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18:499–502.
14. Rollefstad S, Ikdahl E, Hisdal J, Kvien TK, Pedersen TR, Holme I, et al. Systemic inflammation in patients with inflammatory joint diseases does not influence statin dose needed to obtain LDL cholesterol goal in cardiovascular prevention. Ann Rheum Dis 2014. E-pub ahead of print.
15. Semb AG, Rollefstad S, Provan SA, Kvien TK, Stranden E, Olsen IC, et al. Carotid plaque characteristics and disease activity in rheumatoid arthritis. J Rheumatol 2013;40:359–68.
16. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
17. Van der Heijde DM. How to read radiographs according to the Sharp/van der Heijde method [corrected and republished in J Rheumatol 2000;27:261–3]. J Rheumatol 1999;26:743–5.
18. Lukas C, Landewe R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis 2009;68: 18–24.
19. Kadoglou NP, Sailer N, Moumtzouoglou A, Kapelouzou A, Gerasimidis T, Liapis CD. Aggressive lipid-lowering is more effective than moderate lipid-lowering treatment in carotid plaque stabilization. J Vasc Surg 2010;51:114–21.
20. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207.
21. Provan SA, Semb AG, Hisdal J, Stranden E, Agewall S, Dagfinrud H, et al. Remission is the goal for cardiovascular risk management in patients with rheumatoid arthritis: a cross-sectional comparative study. Ann Rheum Dis 2011;70:812–7.
22. Midtbo HB, Gerdts E, Kvien TK, Olsen IC, Hirth A, Davidsen ES, et al. Disease activity and left ventricular structure in patients with rheumatoid arthritis. Rheumatology (Oxford) 2015;54:511–9.
23. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670–81.
24. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, et al, for the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial [published erratum appears in JAMA 2005;294:3092]. JAMA 2005;294:2437–45.
25. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352:1425–35.
26. Semb AG, Kvien TK, DeMicco DA, Fayyad R, Wun CC, LaRosa JC, et al. Effect of intensive lipid-lowering therapy on cardiovascular outcome in patients with and those without inflammatory joint disease. Arthritis Rheum 2012;64:2836–46.
27. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA 2004;291:1071–80.
28. Gonzalez-Gay MA, Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Miranda-Filloy JA, Llorca J. Insulin resistance in rheumatoid arthritis: the impact of the anti-TNFα therapy. Ann N Y Acad Sci 2010;1193:153–9.
29. Tam LS, Tomlinson B, Chu TT, Li TK, Li EK. Impact of TNF inhibition on insulin resistance and lipids levels in patients with rheumatoid arthritis. Clin Rheumatol 2007;26:1495–8.
30. Westlake SL, Colebatch AN, Baird J, Kiely P, Quinn M, Choy E, et al. The effect of methotrexate on cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. Rheumatology (Oxford) 2010;49:295–307.
31. Westlake SL, Colebatch AN, Baird J, Curzen N, Kiely P, Quinn M, et al. Tumour necrosis factor antagonists and the risk of cardiovascular disease in patients with rheumatoid arthritis: a systematic literature review. Rheumatology (Oxford) 2011;50:518–31.
32. Greenberg JD, Kremer JM, Curtis JR, Hochberg MC, Reed G, Tsao P, et al. Tumour necrosis factor antagonist use and associated risk reduction of cardiovascular events among patients with rheumatoid arthritis. Ann Rheum Dis 2011;70:576–82.
33. Ramonda R, Puato M, Punzi L, Rattazzi M, Zanon M, Balbi G, et al. Atherosclerosis progression in psoriatic arthritis patients despite the treatment with tumor necrosis factor-α blockers: a two-year prospective observational study. Joint Bone Spine 2014; 81:421–5.
34. De Groot E, Hovingh GK, Wiegman A, Duriez P, Smit AJ, Fruchart JC, et al. Measurement of arterial wall thickness as a surrogate marker for atherosclerosis. Circulation 2004;(23 Suppl 1): III33–8.
35. Smilde TJ, van Wissen S, Wollersheim H, Trip MD, Kastelein JJ, Stalenhoef AF. Effect of aggressive versus conventional lipid lowering on atherosclerosis progression in familial hypercholesterolaemia (ASAP): a prospective, randomised, double-blind trial. Lancet 2001;357:577–81.
36. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. N Engl J Med 1987;316:1371–5.
37. Johri A, Hetu MF, Nambi V. Carotid plaque or CIMT: what is the future for carotid US imaging? Curr Cardiovasc Risk Rep 2014;8:1–8.
38. Wyman RA, Mays ME, McBride PE, Stein JH. Ultrasound-detected carotid plaque as a predictor of cardiovascular events. Vasc Med 2006;11:123–30.
39. Naqvi TZ, Lee MS. Carotid intima-media thickness and plaque in cardiovascular risk assessment. JACC Cardiovasc Imaging 2014;7:1025–38.