Disease Factors in Early Rheumatoid Arthritis Are Associated with Differential Risks for Cardiovascular Events and Mortality Depending on Age at Onset: A 10-year Observational Cohort Study

Sofia Ajeganova, Maria L.E. Andersson, Johan Frostegård, and Ingiäld Hafström

ABSTRACT. ***Objective.*** To investigate, within the first 2 years of diagnosis with rheumatoid arthritis (RA), associations between disease-related measures and cardiovascular disease (CVD) and mortality in patients with RA onset before and after 65 years of age.

Methods. The study population (n = 741; 67.5% women) was derived from the Better Anti-Rheumatic Pharmaco Therapy (BARFOT) early RA cohort, recruited 1993-1999. The mean age was 55 years (SD 14.7). The outcomes were incident CVD events and all-cause mortality until 2010. Area under the curve (AUC) for disease measures at inclusion, 1 and 2 years, and decrease in measures after 1 year were calculated.

Results. In all, 177 CVD events and 151 deaths occurred over 10 years of observation. In adjusted Cox regression analyses, seropositivity for rheumatoid factor (RF) or anticitrullinated protein antibodies (ACPA); white blood (cell) count at diagnosis; and AUC of C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and visual analog scale (VAS)-pain were associated with higher CVD risk among patients with disease onset before 65 years of age. Among patients with disease onset after 65 years, larger decreases in CRP, ESR, health assessment questionnaire (HAQ), and use of methotrexate decreased CVD risk, whereas use of glucocorticoids heightened CVD risk. AUC of CRP, ESR, HAQ, and HAQ after 2 years was related to risk of death in both age groups. Seropositivity and AUC for VAS-pain in the younger group and use of glucocorticoids in the elderly were associated with poorer survival.

Conclusion. Early treatment of RA may improve longterm outcomes. Presence of RF or ACPA associates with CVD and mortality among RA patients with disease onset before 65 years. Age stratification may improve evaluation of risk for CVD and mortality in early RA. (First Release Aug 15 2013; J Rheumatol 2013;40:1958–66; doi:10.3899/jrheum.130365)

Key Indexing Terms:

RHEUMATOID ARTHRITIS | DISEASE MEASURES | AUTOANTIBODY
CARDIOVASCULAR EVENT | PROGNOSIS | MORTALITY RISK

From the Unit of Rheumatology, Department of Medicine, Karolinska Institute at Karolinska University Hospital Huddinge, Stockholm; R and D Centre, Spenshult Hospital for Rheumatic Diseases, Oskarström and Department of Clinical Sciences, Section of Rheumatology, Lund University, Lund; Unit of Immunology and Chronic Disease, Institute of Environmental Medicine, Karolinska Institute, Stockholm; Unit of Rheumatology, Department of Medicine, Karolinska Institute at Karolinska University Hospital Huddinge, Stockholm, Sweden.

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S. Ajeganova, MD, PhD, Unit of Rheumatology, Department of Medicine, Karolinska Institute at Karolinska University Hospital Huddinge; M.L.E. Andersson, BSc, PhD, R and D Center, Spenshult Hospital for Rheumatic Diseases, Oskarström and Department of Clinical Sciences, Section of Rheumatology, Lund University; J. Frostegård, MD, PhD, Professor, Unit of Immunology and Chronic Disease, Institute of Environmental Medicine, Karolinska Institute; and I. Hafström, MD, PhD, Professor, Unit of Rheumatology, Department of Medicine, Karolinska Institute at Karolinska University Hospital Huddinge.

Address correspondence to Dr. S. Ajeganova, Unit of Rheumatology, R92, Karolinska University Hospital, Huddinge, 141 86 Stockholm, Sweden. E-mail: sofia.ajeganova@karolinska.se

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Rheumatoid arthritis (RA) is associated with an enhanced risk of cardiovascular disease (CVD). Relative to the general population, this risk is estimated to be 2–3 times greater[1]. Overall, RA increases the risk of death due to cardiovascular causes by up to 50% to 60%[2]. Traditional cardiovascular risk factors, chronic inflammation, and treatments of RA are involved in the development of CVD in these patients, and the accelerated atherosclerotic CVD occurs early in the disease process[3].

Despite the high burden of inflammation during the course of RA, several studies have failed to demonstrate the predictive ability of disease measures for subsequent CVD events or mortality. Thus, results from cross-sectional and inception cohort studies are inconsistent[4]. The varying results may depend on study design, e.g., epidemiological studies cannot provide sufficient information on disease-related factors, and cross-sectional studies, including mostly highly heterogeneous patient populations, can generally distinguish only large effects and lack

cumulative measures of disease. Inception cohort-based studies have the potential to examine the role of disease-specific factors during the first critical years after diagnosis for subsequent adverse events.

Baseline markers predictive of clinical outcomes such as destructive joint pathology, comorbidities, and premature mortality might dissociate from the clinical course through appropriate treatment[5,6,7]. Thus, the possibility that better early disease control could confer CVD and survival benefits is appealing. Accumulated evidence from longitudinal inception cohort studies suggests that the course of RA is established early, and that the most important period for therapy is in the first 1–2 years. To date, few reports have shown relationships between the early changes in inflammatory and RA disease measures and irreversible clinical complications[8].

Further, RA is a complex disease with a high degree of clinical heterogeneity and different phenotypes due to sex, age at onset, autoantibodies, and genotype[9]. Still, the literature on outcomes in subgroups of patients with RA is sparse.

Therefore, we studied the associations of disease-related factors during the first 2 years after diagnosis of RA to incident CVD morbidity and all-cause mortality, and whether the effect of these factors differs between patient groups depending on age at disease onset.

MATERIALS AND METHODS

We used data from an established early RA cohort, Better Anti-Rheumatic Pharmaco Therapy (BARFOT)[10], a multicenter prospective observational study covering urban and rural patient referral areas. The inclusion criteria were RA diagnosis according to the American College of Rheumatology definition[11], age > 18 years, and disease duration ≤ 12 months. We identified the participants who were consecutively recruited from 1993 through 1999 (n = 861). Individuals were excluded from participation if they had prevalent CVD at RA diagnosis, such as acute myocardial infarction, unstable angina, coronary and vascular surgery, heart failure, atrial fibrillation, peripheral arterial disease, stroke, and transient ischemic attack (n = 113). Also excluded were patients younger than 20 years (n = 7). Our final study population consisted of 741 patients with early RA.

All study participants provided written informed consent. The study was approved by the regional ethics committee in Stockholm, Sweden, and was performed in accordance with the Declaration of Helsinki.

Assessment of RA disease and risk factors. Demographics, medical history, smoking status, anthropometric data, and laboratory data were obtained from the BARFOT database. RA disease activity was calculated using the Disease Activity Score for 28 joints (DAS28) with erythrocyte sedimentation rate (ESR)[12]. Functional status was self-assessed by the validated Swedish version of the Stanford Health Assessment Questionnaire (HAQ), range 0–3[13]. The patients were started with disease-modifying antirheumatic drugs (DMARD) in accordance with the recommended treatment strategy in Sweden. Information on antirheumatic medication was collected through the BARFOT registry. Regular use of methotrexate (MTX), biologic agents, and glucocorticoids (GC) was considered if it was reported for at least 6 months throughout the followup.

Non-high-sensitive C-reactive protein (CRP) and white blood (cell) count (WBC) were estimated by the standard methods used at each center. Aliquots of plasma and serum were stored at –70°C until further analysis. Sera from study enrollment were analyzed for immunoglobulin (Ig)M rheumatoid factor (RF) using an agglutination test (Serodia; Fujirebio); a titer of > 20 IU/ml was regarded as positive. Anticitrullinated protein antibody (ACPA) was determined using an ELISA CCP2 test (Euro-Diagnostica). Positive ACPA was defined as a titer > 25 U/ml.

Smoking status at inclusion was self-reported as daily, ever smoking (current or past), or never smoking. Information on traditional CVD risk factors, such as hypertension, diabetes mellitus, and hyperlipidemia, was collected at inclusion and up to the date of the outcome or at the end of the followup through discharge diagnosis from hospital admissions and the BARFOT registry.

Outcome assessment. The outcomes were a composite incident CVD event (i.e., fatal or nonfatal myocardial infarction, angina pectoris, coronary bypass grafting or percutaneous coronary intervention, peripheral arterial disease, vascular surgery, ischemic stroke, transient ischemic attack) and all-cause mortality. CVD events were defined using the International Classification of Diseases, 9th ed (ICD-9) and ICD-10 codes: 410, 411, 413, 427F, 433-436, 440-444, 3066-3067, 3080, 3092, 3105, 3127, 3141, 3158, 88, 0961-0964, I20-21, Y832, I46, I63-I66, G45, I70-I72, I73.9, and I74.

The observation period was July 1993 to October 1999, i.e., when the patients were included in the BARFOT study. The followup lasted until occurrence of the first-ever incident CVD event, death, or to December 2010. Morbidity data were obtained from the Swedish Hospital Discharge Registry, between January 1987 and December 2010. Survival confirmation, date, and cause of death were obtained from the National Cause of Death Registry.

The registries have nationwide coverage and are effectively complete, because reporting of data is obligatory in Sweden. In our study, registry records were randomly checked for quality of data by comparing them with complete medical records (137 out of 861 patients). The registry data were found to be > 97% diagnostically accurate.

Statistical analysis. The baseline features were compared using the t test, Mann-Whitney U test, or Wilcoxon rank test for continuous variables, and the chi-square or the Fisher's exact tests for categorical variables between groups of outcomes as well as age at onset groups. The Spearman test was used to examine correlations.

Incidence rates of CVD (with the 95% CI for a Poisson count) were presented as events per 100 person-years at risk, performed separately for the study outcomes.

Area under the curve (AUC) using the trapezoidal rule was calculated for the disease measures assessed at inclusion and after 1 and 2 years. Reduction in the disease measures between inclusion and 1 year after enrollment was calculated. Data on clinical characteristics during followup were missing in < 3%, and imputation was not applied.

Disease predictors of interest, collected at inclusion and after 1 and 2 years, were tested in Cox proportional hazard models. Unadjusted models were analyzed first, followed by multivariate models, entry procedure with $p < 0.10$ criterion. Multivariate models were chosen *a priori* to adjust for age, sex, and traditional CVD risk factors. Stratified analyses within age groups (< 65 and ≥ 65 yrs old at RA onset) were applied. Age-grouping was done according to the distribution of outcomes over the age strata and was carried out before the Cox analyses. Cases with a CVD event within 2 years of enrollment were excluded from analyses for correct interpretation of prognostic Cox regression models: 9 cases for changes in measures during the first year of observation (2 and 7 patients at younger and older age at disease onset, respectively), and 16 cases for AUC measures during the first 2 years in analysis of CVD risk (4 and 12 patients at younger and older age at disease onset, respectively); none had died before 2 years of followup.

A 2-tailed $p < 0.05$ was considered significant. Statistical analyses were done using computer software (IBM SPSS, version 20; SPSS Inc.).

RESULTS

During the median observation time of 13 years (range 2–17), corresponding to 9405 person-years of followup, 177 patients had a first CVD event and 151 died (causes of death

related to CVD in 50% and malignancy in 35%; Table 1). Of the CVD events, 94 were related to ischemic coronary heart disease, 22 to ischemic peripheral arterial disease, and 65 to episodes of ischemic cerebrovascular disease (2 different cause-specific CVD conditions were registered at discharge in 4 cases). During the course of RA, occurrence of the first CVD event was generally constant, with 34% occurring before 5 years of disease, and 41% and 25% of events during 5–10 years and > 10 years of followup, respectively. As to all-cause mortality, 10% occurred within the first 5 years of followup, and 50% and 40% during 5–10 years and > 10 years of followup, respectively. Participants who developed a CVD event during the study were older at enrollment and more likely to be men, hypertensive, or to have diabetes. They had higher CRP and WBC but were less likely to be prescribed DMARD than those with no CVD. Patients who had died had baseline characteristics similar to those with CVD, except that they were smokers and RF-positive more often, and had higher measures of ESR and HAQ than did those who had not died (Table 2).

During followup, the prevalence of hypertension, diabetes, and hyperlipidemia was higher among individuals with adverse study outcomes. Similarly, the inflammatory burden up to 2 years after diagnosis measured by AUC of CRP and ESR was higher. Functional ability was worse among those who died (Table 3). Participants with adverse outcomes were less likely to be treated with MTX regularly, and those who died were less likely to be treated with biologic agents. Individuals who experienced a CVD event had been more frequent users of GC.

Risk factors for incident CVD events and mortality outcomes. The results of the Cox regression models are presented in Table 4. In analyses adjusted for age, sex, and traditional CVD risk factors, increased risk for incident CVD events was associated with higher HAQ after 2 years and regular use of GC. Decreased CVD risk was associated with reduction in HAQ, use of any DMARD and MTX during the first year, or regular use of MTX after the first year. Higher death rates were independently related to RF positivity, higher WBC and HAQ score at baseline, AUC of CRP, ESR, DAS28, and HAQ, as well as HAQ after 2 years. Conversely, lowered mortality risk was independently associated with reduction in visual analog scale (VAS) pain and use of biologic agents.

Participants who experienced CVD events within 2 years after RA diagnosis were older and it could be suggested that their exclusion could bias results, but these patients made up very few cases and additional analyses including all cases were unchanged.

Stratification of outcomes by age at RA disease onset. Disease characteristics in patients < 65 years and ≥ 65 years of age at RA onset were similar with regard to RF positivity, WBC, VAS pain, and the HAQ scores at baseline. At RA diagnosis, symptoms of joint disease were recognized to have lasted for a mean of 6.6 months (SD 3) in the younger group, and 5.8 months (3) in the older group. Further, HAQ after 2 years; frequency of use of DMARD, MTX, and GC during the first year; and regular use of GC during observation did not differ between the age groups. However, the older participants, compared to the younger ones, were ACPA-positive less often; they had higher baseline measures of CRP, ESR, and DAS28 and were treated less often with MTX or biologic agents. Among patients with RA onset before the age of 65, RF or ACPA positivity, AUC of CRP, ESR, and VAS pain were independently associated with an increased risk of CVD event, as shown in Figure 1A. Among patients with RA onset after 65 years, improved CVD prognosis was related to reductions in CRP, ESR, and HAQ during the first year, and regular use of MTX, while regular use of GC worsened CVD outcome.

These variables were associated with an increased risk of death in the group with younger RA onset: positive RF or ACPA, higher WBC at baseline, and AUC of VAS pain over the first 2 years. Among patients over 65 years at RA onset, AUC of DAS28, fewer reductions in DAS28, and VAS pain after 1 year were associated with an increased risk of death (Figure 1B). In both age groups, higher AUC of CRP, ESR, and HAQ, as well as HAQ score after 2 years were independently and significantly associated with poorer survival.

Table 1. Rates of the study outcomes (per 100 person-years) throughout the observation period, grouped by age (years) at inclusion.

Study Outcomes	Number of Events, 95% CI	Person-years of Observation	Rate per 100 Person-years 95% CI
Incident CVD event	177 (150.9–203.1)	8324	2.1 (1.8–2.4)
< 65 years	67 (62.8–71.2)	6470	1.0 (1.0–1.1)
≥ 65 years	110 (104.6–115.4)	1854	5.9 (5.6–6.2)
All-cause mortality	151 (126.9–175.1)	9140	1.7 (1.4–1.9)
< 65 years	52 (37.9–66.1)	6802	0.8 (0.6–1.0)
≥ 65 years	99 (79.5–118.5)	2338	4.2 (3.4–5.1)

CVD: cardiovascular disease.

DISCUSSION

We report that among patients with early RA, inadequate control of systemic rheumatoid inflammation is associated with CVD-related hospitalization and survival. Participants in our study had symptom duration of about 6 months at diagnosis; they were diagnosed during the 1990s and followed for more than 10 years. The finding emphasizes the significance of cumulative inflammation for CVD and mortality outcomes in RA, as well as the detrimental role of insufficient treatment of RA during the critical period after diagnosis. Further, in ages < 65 years at disease onset, RF or ACPA positivity, a higher WBC at baseline, and sustained VAS pain were unfavorable for CVD outcome. Use of any

Table 2. Characteristics of rheumatoid arthritis patients at disease onset, grouped by occurrence of cardiovascular disease (CVD) event and all-cause mortality during followup.

	All, n = 741	Incident CVD Event		All-cause Mortality	
		Yes, n = 177	No, n = 564	Died, n = 151	Survived, n = 590
Age, years	55.0 ± 14.7	65.9 ± 11.8***	51.5 ± 13.8	67.5 ± 11.4***	51.8 ± 13.7
Females, %	67.5	55.9***	71.1	57.0**	70.2
Smoking ever vs never, %	58.7	59.9	58.3	68.9**	56.1
Hypertension, %	16.7	31.6***	12.1	28.5***	13.7
Diabetes mellitus, %	5.1	9.3**	3.8	9.5**	3.9
Hyperlipidemia, %	0.8	1.7	0.5	2.0	0.5
RF positivity, %	59.5	62.9	58.3	67.6*	57.3
ACPA positivity, %	55.5	53.3	56.2	56	55.4
CRP, mg/l	19 (6–46)	23 (10–54)**	17 (6–43)	27 (12–59)***	17 (6–42)
ESR, mm/h	36 ± 26	38 ± 25	35 ± 27	41 ± 26**	34 ± 26
WBC	8.2 ± 2.6	8.7 ± 2.7**	8.1 ± 2.6	8.9 ± 2.9***	8.0 ± 2.5
DAS28	5.1 ± 1.3	5.1 ± 1.3	5.1 ± 1.3	5.2 ± 1.4	5.1 ± 1.2
HAQ	0.99 ± 0.62	1.0 ± 0.67	0.98 ± 0.60	1.09 ± 0.70*	0.96 ± 0.59
VAS pain, mm	45.3 ± 24.1	45.0 ± 25.5	45.4 ± 23.6	43.8 ± 26.4	45.7 ± 23.4
DMARD, start, %	84.1	75.7***	86.7	80.8	84.9
MTX, start, %	43.7	39.6	44.8	42.6	43.9
GC, start %	51.4	55.9	50.0	57.6	49.8

Values are mean ± SD or medians (IQR) depending on values distribution. P values for between-group differences: * $p < 0.05$; ** $p \leq 0.01$; *** $p \leq 0.001$. CVD: cardiovascular disease; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibody; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood (cell) count; DAS28: Disease Activity Score in 28 joints; HAQ: Health Assessment Questionnaire; VAS pain: visual analog scale for pain; DMARD: disease-modifying antirheumatic drugs; MTX: methotrexate; GC: glucocorticoids.

DMARD after RA diagnosis and regular use of MTX were associated with less CVD in patients aged 65 and older at disease onset. The use of GC significantly raised the mortality risk in the older group. The results imply that RA disease factors may have differential value for cardiovascular morbidity and all-cause mortality prognoses.

RA may worsen or hasten comorbidity[14]. A hypothesis that should be tested is that tight control of disease activity would dissociate the inflammatory clinical variables at baseline from their predictive value, i.e., dissociation of risk and reality[15]. Here, we demonstrated that the CVD risk in RA could be decreased and survival improved if the RA is managed and treated with appropriate intensity early on. In previous studies, it has been shown that successful suppression of RA activity through antirheumatic treatments may improve markers of CVD risk and reduce CVD risk and mortality[6,7,16,17,18,19,20,21].

Further, we explored the influence of age at RA onset on predictive models of adverse CVD outcome and mortality in early RA. Generally, in the younger patient group, AUC of inflammatory measures over the first 2 years of disease was shown to be associated with the study outcomes. In the older patient group, the changes in the inflammatory markers between baseline and the 1-year assessment were associated with the outcome. In the elderly, inflammation is common and a consequence of many causes; the burden disappears in statistical analyses when adjusted for age, which might explain these differences. Still, CRP-AUC and ESR-AUC were linked to death in both age groups, but numerically the associations were attenuated in the older population. These results imply that different longitudinal approaches may be of importance in studies validating prognostic factors in RA.

The association between age at symptom onset and clinical outcomes may relate to the rate of progression of RA disease and atherosclerosis. Thus, higher age at symptom onset is likely to be associated with a faster rate of increasing morbidity and thus a poorer prognosis. In addition, considering differences in clinical characteristics such as frequency of systemic inflammatory features and seronegativity in older compared with earlier onset indices[22,23,24], clinical identifiers of risk of adverse clinical outcomes may differ according to age. The results of our study, in which the reductions in CRP, ESR, and DAS28 after 1 year were protective in the older age group, suggest that there is a special urgency to get disease activity under control in this age group, which has a lesser ability to cope with inflammation and added disability. To date, cutoffs for "early" and "older" RA disease onset have not been defined, and ranges from 45 to 75 years have been used in previous studies. Our distinction of age groups is similar to earlier reports[25,26] and was based on the frequency of outcomes to make possible the performance of robust Cox regression analyses with multiple adjustments.

The WBC at RA diagnosis, prior to any immunosup-

Table 3. Clinical characteristics of patients throughout the followup, grouped by occurrence of cardiovascular disease (CVD) event and all-cause mortality.

	All, n = 741	Incident CVD Event		All-cause Mortality	
		Yes, n = 177	No, n = 564	Died, n = 151	Survived, n = 590
CVD risk factors					
Hypertension, %	30.2	50.8***	23.8	38.4*	28.1
Diabetes mellitus, %	7.2	11.0*	6.1	12.8**	5.8
Hyperlipidemia, %	8.1	23.2***	3.4	11.3	7.3
Decrease (Δ) in disease measures after 1 year					
ΔCRP, mg/l	8 (0–32)	11 (0–34)	6 (0–31)	13.5 (0–39)	6 (0–30)
ΔESR, mm/h	16.9 ± 24.4	14.8 ± 26.6	17.5 ± 23.7	17.1 ± 26.9	16.8 ± 23.8
ΔDAS28	1.8 ± 1.6	1.7 ± 1.7	1.9 ± 1.6	1.7 ± 1.8	1.9 ± 1.6
ΔHAQ	0.42 ± 0.60	0.35 ± 0.61	0.44 ± 0.60	0.39 ± 0.69	0.43 ± 0.58
ΔVAS pain, mm	17.5 ± 29.7	16.0 ± 31.1	18.0 ± 29.3	13.6 ± 32.2	18.6 ± 29.0
Disease burden (AUC) up to 2 years					
CRP-AUC, mg/l	26 (15–48.5)	32.5 (18–56.5)***	24.5 (13–45)	38 (22–65.5)***	24 (12.5–44)
ESR-AUC, mm/h	38 (22–62)	46 (27–73)***	35 (21–60)	48 (28–79)***	36 (20–60)
DAS28-AUC	7.5 ± 2.3	7.6 ± 2.3	7.4 ± 2.2	7.8 ± 2.4	7.4 ± 2.2
HAQ-AUC	1.36 ± 1.0	1.46 ± 1.09	1.33 ± 0.97	1.64 ± 1.16***	1.29 ± 0.94
VAS pain-AUC, mm	64.6 ± 38.2	65.0 ± 37.8	64.5 ± 38.4	67.2 ± 41.0	64.0 ± 37.5
HAQ at 2 years	0.59 ± 0.59	0.66 ± 0.62	0.57 ± 0.58	0.75 ± 0.67***	0.55 ± 0.57
Regular therapies					
MTX, %	67.2	56.3***	70.6	59.6*	69.1
GC, %	51.8	58.5*	49.7	57.6	50.3
Biologic agents, %	15.9	12.4	17.1	4.6***	18.8

Values are mean ± SD or medians (IQR) depending on values distribution. P values for between-group differences: * $p < 0.05$; ** $p \le 0.01$; *** $p \le 0.001$. CVD risk factors considered if occurred before the study outcomes or the end of observation. AUC: area under the curve calculated on measurements at baseline, after 1 and 2 years; Δ = decrease in measurements between baseline and the 1-yr assessment; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28: Disease Activity Score in 28 joints; HAQ: Health Assessment Questionnaire; VAS pain: visual analog scale for pain; MTX: methotrexate; GC: glucocorticoids.

pressive and GC therapy, but not levels of CRP and ESR, was independently linked to death in the whole study population, and also to a subsequent CVD event in the younger patients. The changes in inflammatory, immunologic variables, and blood cell counts with aging could be one reason for the absence of association with CVD in the older participants[27]. In the general population, prospective studies have demonstrated association between higher WBC and CVD, death after acute coronary syndrome, and all-cause mortality[28,29,30], but this relationship has not been explored in early RA. One cross-sectional study has, however, documented that the WBC, independent of age, sex, and disease duration, was predictive of mortality in patients with RA[31]. Mononuclear cells play a central role in the pathogenesis of atherosclerosis, and the proliferative activity of these cells can be increased by relatively mild systemic inflammatory stimuli[32]. Additional studies are warranted to link WBC to CVD and mortality risk in RA.

In our analyses, associations between RF, ACPA positivity, and adverse outcomes were present in the participants aged < 65 years at diagnosis, but not in the elderly. Previously, positivity for RF and/or ACPA, together with traditional CVD risk factors, have been reported to contribute to prediction of CVD events and/or death in healthy individuals[33,34,35] and in patients with RA[36] or rheumatic diseases[35,37], while other studies failed to detect these associations[38,39]. The inconsistency of the role of seropositivity for predicting clinical outcomes in RA may depend on variety of age and absolute risk of the outcome in the studied populations, as well as the degree to which other risk factors are included in analyses. Studies in which predictive associations with the CVD or mortality outcome were reported tend to include relatively young participants[40], while an absence of an association may reflect the older age group and heavy risk factor burden in the predominantly small-sized cohorts[41].

Knowledge is limited of the effect of pain and HAQ score and their changes early in the RA course on future CVD and mortality[42]. In our study, we found that in the whole cohort, the higher the reduction in the VAS pain score after 1 year, the lower the estimated mortality risk. Also, the higher the reduction in the HAQ score, the lower the risk for incident CVD. Among younger patients, similar to measures of inflammatory burden, VAS pain-AUC was independently associated with enhanced mortality. The HAQ score measure after 2 years and HAQ-AUC were associated with mortality in all ages. Our findings and the recent report on the lowest probability of longterm disability if persistent

Table 4. Predictors of cardiovascular disease (CVD) and mortality over 10 years.

Factors	Incident CVD Event No.	Incident CVD Event HR (95% CI)	Incident CVD Event p	All-cause Mortality No.	All-cause Mortality HR (95% CI)	All-cause Mortality p
Baseline measures						
RF positivity	107	1.2 (0.88–1.64)	0.2	96	1.61 (1.13–2.31)†	0.009
CRP, per 10 mg/l	174	0.99 (0.96–1.03)†	0.7	147	1.02 (0.98–1.06)†	0.3
WBC	167	1.04 (0.98–1.10)†	0.2	142	1.07 (1.00–1.13)†	0.046
HAQ	174	1.09 (0.85–1.40)	0.5	146	1.35 (1.04–1.75)†	0.023
Decrease (Δ) in disease measures after 1 year						
ΔHAQ	159	0.75 (0.58–0.97)†	0.029	143	0.90 (0.67–1.19)	0.4
ΔVAS pain, per 10 mm	158	0.98 (0.93–1.03)	0.4	147	0.93 (0.88–0.99)†	0.015
Measure of disease burden (AUC) up to 2 years						
CRP-AUC, per 10 mg/l	148	1.04 (1.00–1.08)†	0.077	137	1.08 (1.04–1.12)†	0.000
ESR-AUC, per 10 mm/h	156	1.02 (0.97–1.07)†	0.4	147	1.06 (1.01–1.10)†	0.012
DAS28-AUC	154	1.02 (0.95–1.09)	0.7	145	1.09 (1.01–1.17)†	0.033
HAQ-AUC	153	1.14 (0.99–1.33)†	0.078	141	1.39 (1.19–1.63)†	0.000
HAQ at 2 years	160	1.35 (1.05–1.73)†	0.019	149	1.75 (1.35–2.27)†	0.000
Therapies the first year						
DMARD	134	0.63 (0.44–0.90)†	0.011	122	0.83 (0.55–1.24)	0.4
MTX	71	0.72 (0.53–0.97)†	0.033	70	0.95 (0.69–1.31)	0.8
Regular therapies during followup						
MTX	93	0.72 (0.53–0.99)†	0.043	90	0.99 (0.71–1.38)†	0.9
GC	98	1.65 (1.21–2.26)†	0.002	87	1.24 (0.90–1.71)	0.19
Biologic agents	21	1.32 (0.83–2.10)†	0.2	7	0.45 (0.21–0.98)†	0.045

Presented are unadjusted HR for analyses with nonsignificant results. Adjusted HR† were run if results of the crude analyses showed a $p < 0.10$. Multivariate models are adjusted for age, sex, smoking status at inclusion, and hypertension, diabetes mellitus, and hyperlipidemia registered throughout the observation period. RF: rheumatoid factor; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; AUC: area under the curve; WBC: white blood (cell) count; DAS28: Disease Activity Score in 28 joints; HAQ: Health Assessment Questionnaire; VAS pain: visual analog scale for pain; DMARD: disease-modifying antirheumatic drugs; MTX: methotrexate; GC: glucocorticoids.

remission is achieved[43] highlight the concern about pain and functional impairment in early RA.

The findings here largely confirmed and broadened the previous reports on the protective value of antirheumatic treatments[44,45]. Thus, use of any DMARD in the first year after diagnosis and regular use of MTX > 6 months during observation were linked to better CVD outcomes in the whole cohort and in the older participants, independent of demographic variables and traditional CVD risk factors. Use of biologic agents was associated with a decrease in the estimated mortality risk, a result that cannot, however, be considered definite, owing to confounding by indication/contraindication and a low number of events in analysis. The possibility of better survival as a result of effective control of systemic inflammation is, however, worth bearing in mind[46].

The effect of GC on the risk of CVD and increased mortality in patients with RA is being debated, and both beneficial and harmful effects have been recognized[47,48]. In our study, low-dose oral GC, prednisolone up to 10 mg/day, the first year after RA diagnosis, and its continuous use > 6 months during followup, were equally prescribed to younger and older patients in addition to standard therapy. GC use in the first year heightened the risk of incident CVD in the older age group, and a trend toward higher mortality risk was also found. Regular GC use during followup was also associated with increased risk for incident CVD in the elderly. The findings here thus support the evidence linking low-dose GC therapy with adverse clinical outcomes in elderly patients with RA, but we acknowledge possible confounding by indication.

The potential strengths and limitations of our study merit consideration. Its principal strengths are structured measurement of a broad range of markers over the first 2 years after RA diagnosis, the complete followup over a substantial time period, and reliable data sources. The study population involved a typical early RA cohort treated with conventional care. The validity of our measurements is demonstrated by reasonable incidence rates of the outcomes and distribution of several established CVD risk factors, which were generally similar to those previously reported in other western early RA populations[2,49,50]. This study was prospective in patient enrollment and followup, but was observational in nature and subject to limitations, such as uncorrected confounding and confounding by indication. Thus, total dose and duration of antirheumatic therapy and cumulative drug exposure were unavailable. Further, only information on lipid-lowering treatment was available rather than measures of blood lipids. We used the composite CVD outcome; thus the reported associations cannot be extrapolated for specific coronary, cerebrovascular, or peripheral atherosclerotic events. Reporting effects of therapies, we

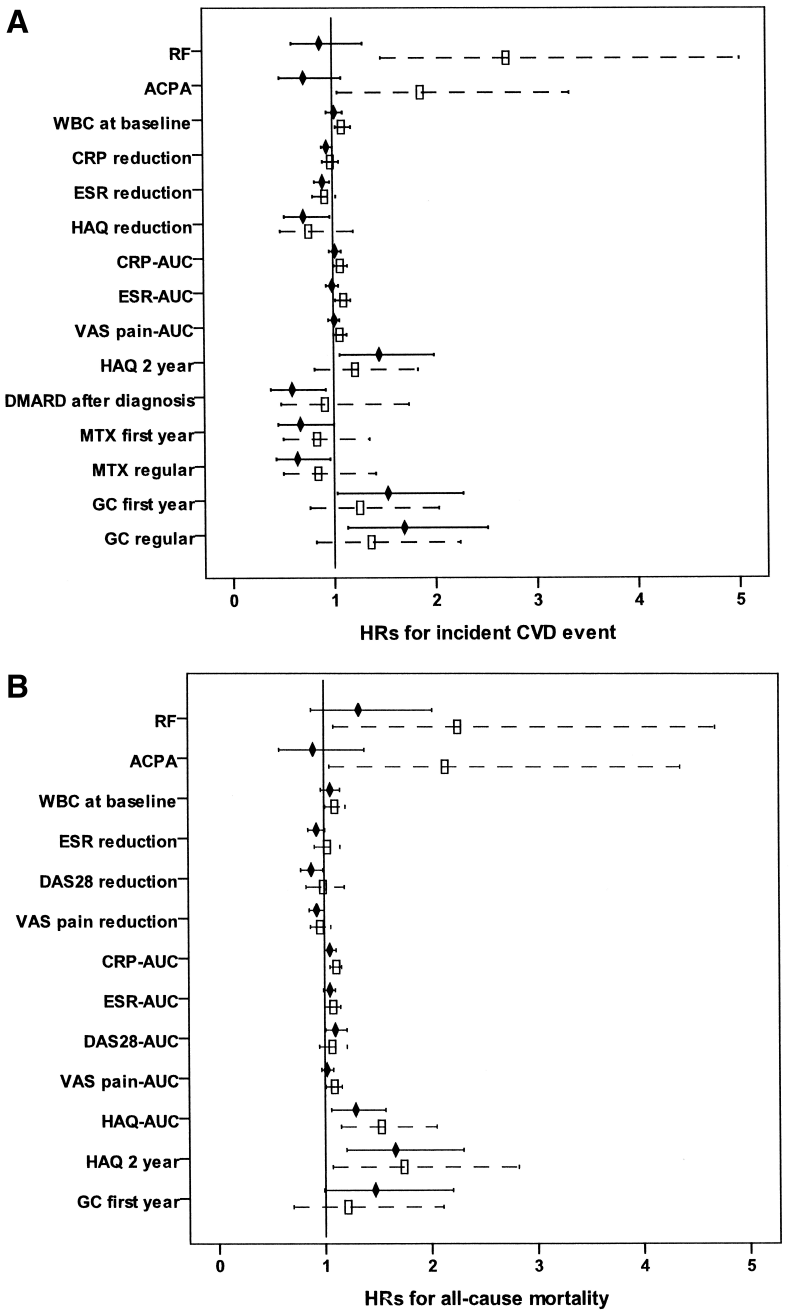

Figure 1. Association of disease factors with risk of incident cardiovascular disease (CVD) event (A), and all-cause mortality (B) in prespecified groups of patients aged ≥ 65 (diamonds and solid lines) and < 65 (hollow squares and dotted lines) at the study enrollment. Shown are HR with the 95% CI as calculated by Cox proportional regression models, adjusted for age, sex, smoking status, hypertension, diabetes mellitus, and hyperlipidemia. Area under the curve (AUC) was calculated based on measurements at baseline, after 1 and 2 years, and reduction (change between measurements at baseline and after 1 year). Presence of rheumatoid factor (RF) and anticitrullinated protein antibodies (ACPA), use of methotrexate (MTX), disease-modifying antirheumatic drug (DMARD), and glucocorticoids (GC) are used as dichotomous variables. WBC: white blood (cell) count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; VAS: visual analog scale; DAS28: Disease Activity Score in 28 joints.

acknowledge a possibility of confounding by indication, because patients who present with RA at an advanced age may be treated differently, owing to comorbidities. However, in our study, the frequency of use of DMARD, MTX, and GC during the first year after enrollment, and regular use of GC during the followup, did not differ between the age groups. Thus, at least in the beginning of the RA disease, any comorbidity in the elderly in our cohort did not affect the choice of antirheumatic medication.

This prospective early RA cohort study suggests that better control of systemic rheumatoid inflammation during the critical first years of disease may confer cardiovascular and survival benefits in patients with early RA. Further, it extends the knowledge about the predictive value of the inflammatory variables in younger and older disease onset, which raises the possibility of specific interventions to reduce CVD morbidity and all-cause mortality in RA. Further clarification of the link between inflammation, disease markers, and therapies with adverse clinical outcomes is required with more precise quantification of association in particular subgroups, such as sex, age, and autoantibody pattern.

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