EXTENDED REPORT

Low disease activity (DAS28≤3.2) reduces the risk of first cardiovascular event in rheumatoid arthritis: a time-dependent Cox regression analysis in a large cohort study

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ABSTRACT

Objective Systemic inflammation appears to contribute to the excess risk of cardiovascular disease (CVD) in rheumatoid arthritis (RA). The objective of this study was to investigate the effect of different levels of disease activity over time, particularly low disease activity and remission, on CVD risk in patients with RA.

Methods Data from the Nijmegen early RA inception cohort were used. The primary outcome was first CVD events within the first 10 years of follow-up. Cut points of the DAS28 for remission (<2.6) and low (≤3.2), moderate (3.2–5.1) and high (>5.1) disease activity were used. The effect of disease activity on CVD risk was analysed using Cox-proportional hazards regression with DAS28 as a time-dependent covariate and also conventionally with time-averaged DAS28 as the primary dependent variable.

Results Low DAS28 (≤3.2) was significantly associated with a reduced risk of CVD (HR 0.65, 95% CI 0.43 to 0.99) compared with DAS28 >3.2, both when included as a time-dependent covariate and as time-averaged DAS28 ≤3.2 (HR 0.52, 95% CI 0.33 to 0.81). Remission had a modest, non-significant protective effect against CVD (HR 0.67, 95% CI 0.43 to 1.07).

Conclusion Results of this study suggest that low disease activity is sufficient to achieve a protective effect against CVD in RA. Apparently, remission defined as DAS28 <2.6 has no additional protective effect against CVD compared with low disease activity. Our results strengthen the use of tight control strategies in daily clinical practice to achieve low stable disease activity or remission in patients with RA as soon as possible.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease that affects 0.5–1% of the population.[1] Patients with RA have an increased risk of cardiovascular disease (CVD).[2 3] Evidence suggests that the increased CVD risk is partly mediated by systemic inflammation, a characteristic for RA, in addition to traditional risk factors Inflammation may alter the effect of existing CVD risk factors or factors protective for CVD, leading to an increased risk of CVD.[4–6] Furthermore, inflammation may accelerate the atherosclerotic process[7 8] and lead to the formation of more severe coronary and carotid atherosclerotic plaques in patients with RA.[9–12] In comparison to healthy controls and patients with RA in remission, patients with active disease seem to have more unstable plaques, increasing the probability of CVD.[13] Consequently, the level of disease activity has been implicated as a contributing factor to the development of CVD. Conversely, clinical remission or the absence of inflammation may be associated with a reduced risk of CVD in RA. However, there is conflicting evidence concerning the association between the level of disease activity and CVD risk. The results from a case-control study showed no evidence that disease activity over time was associated with occurrence of myocardial infarction.[14] In another longitudinal study by our group, results indicated that very high disease activity over time or high disease activity at RA onset significantly contributes to the risk of CVD in RA.[15] In a recent study by Myasoedova *et al*, it was demonstrated that particularly exposure to disease activity flare-ups and increased cumulative burden of RA disease activity seems to contribute to this risk.[16] Furthermore, patients with active RA have significantly increased levels of biomarkers for CVD, while patients who were in remission did not.[17] Overall, these findings led to the hypothesis that achieving remission may reduce the risk of CVD in patients with RA. As a clinical consequence, tight control of disease activity could therefore have a beneficial effect on CVD risk.[18] It is unclear whether clinical remission needs to be achieved in order to eliminate or diminish the possible harmful effects of systemic inflammatory activity or if stable low disease activity over time is sufficient. Therefore, the primary objective of this study is to investigate the effect of different levels of disease activity over time, particularly low disease activity, on CVD risk in patients with RA. Second, the effect of remission over time on the risk of CVD is investigated.

PATIENTS AND METHODS

Study design and patients

The prospectively collected data from the Nijmegen early RA inception cohort were used. Patients were included at diagnosis of RA (baseline) in the outpatient clinic of the departments of rheumatology of the Radboud University Medical Centre (since 1985) or the Maartenskliniek in Nijmegen (since 1990). Patients with RA who fulfilled the 1987 American College of Rheumatology (ACR) (inclusion before 2010) or ACR/European League Against

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Rheumatism (EULAR) 2010 (inclusion after 2010) criteria for the classification of RA,[19] with disease duration of <1 year and who were disease modifying anti-rheumatic drug (DMARD) naïve, were included. All patients received written patient information and gave written informed consent. According to Dutch law and regulations, ethical review was not necessary for this observational study. Patients with confirmed CVD before inclusion and patients with a follow-up <12 months or patients with two or less DAS28 measurements were excluded for the current analyses. All disease activity measurements that were taken between the date of inclusion in the cohort and the date of a first CVD event or censoring were included in the analysis, with a maximum of 10 years of follow-up.

Data collection

The patients were seen during scheduled visits every 3–6 months. During these visits, disease activity was measured using the DAS28.[20 21] Baseline variables were retrieved from the cohort database: age (years), gender (male/female), rheumatoid factor (RF) positivity, anti-cyclic citrullinated peptide (anti-CCP) positivity, erythrocyte sedimentation rate (mm/hour) and C-reactive protein (CRP) (mg/L), Swollen Joint Count (SJC28), Tender Joint Count (TJC28) and the patient Visual Analogue Score for global disease activity (VAS), DAS28 and Health Assessment Questionnaire (HAQ). Data on traditional CVD risk factors at baseline were collected by review of medical charts and electronic patient files, including current smoking status (Y/N), blood pressure (mm Hg), height (m), weight (kg), diabetes mellitus (Y/N), hypertension (Y/N) and family history of CVD (Y/N). Non-fasting total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-c) concentrations (mmol/L) were measured using serum from frozen samples collected at baseline at laboratory facilities of Russells Hall Hospital, Dudley UK.[22]

Primary outcome

The primary outcome was occurrence of a first CVD event (physician diagnosed fatal or non-fatal cases of CVD), as retrieved from the database, by extensive review of medical charts and electronic patient files. The following were classified as CVD events: acute coronary syndrome, stable angina pectoris, cerebral vascular accident (CVA), transient ischaemic attack (TIA), peripheral artery disease and heart failure. Deaths due to CVD were verified from death certificates, provided by Statistics Netherlands,[23] including deaths due to CVD and CVA but excluding cerebral haemorrhage and non-coronary cardiac death.

Statistical analysis

Baseline variables were compared between the CVD event group and the non-event group by means of independent samples t-test, Wilcoxon or χ^2 statistics. The cut-off value for low disease activity was defined as DAS28 ≤3.2 and that for clinical remission was defined as DAS28 <2.6.[20 21 24] A Cox-proportional hazard regression model was chosen as the primary analysis. First, three analyses were performed with disease activity as the segmented time-dependent covariate and time to first CVD event (or disease duration) as the primary outcome. This type of analysis is suited to avoid bias introduced by analysing time course (non-baseline) variables in combination with survival time. Disease activity was added as a continuous variable and as a dichotomous variable: low disease activity (yes/no) or clinical remission (<yes/no). Disease activity was measured regularly, every 3–6 months, and a 6 month interval was maintained for the time-dependent covariate in the Cox-proportional hazard regression analyses. These time segments corresponded with DAS28 measurements at 6 month intervals. In case of one isolated missing measurement, the mean of the measurement prior and the measurement following the missing value was used. If more than one consecutive measurement was missing, subjects were censored. To repeat the analysis using a more readily interpretable reflection of disease activity, the next step was to analyse the time-averaged DAS28 as main dependent variable using conventional Cox-proportional hazard regression analysis. The time-averaged DAS28 was calculated by taking the area under the curve of the DAS28 score of the total follow-up period divided by the follow-up period. The analysis was performed again with the time-averaged DAS28 as a binary variable (time-averaged DAS28 ≤3.2 or 2.6).

In all analyses, sex and age were included in the model as confounders by default. The following potential confounders were considered; current smoking status, baseline measurements of systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg) and body mass index (weight (kg)/height (m^2)), hypertension (physician diagnosis), diabetes mellitus (type 1 and 2), TC (mmol/L), HDL-c (mmol/L), family history of premature CVD, use of statins and use of anti-hypertensive medication (diuretics, ACE/angiotensin II inhibitors, beta-blockers or calcium blockers) at baseline, RF status, anti-CCP status, baseline DAS28, CRP and HAQ. Additionally, the effect of both remission and of low DAS28 over time on survival for CVD was assessed using Kaplan-Meier survival analysis. First, subgroups were made based on the time-averaged DAS28: remission (DAS28 <2.6), low (DAS28 2.6–3.2), intermediate (DAS28 3.2–5.1) and high (DAS28 >5.1). In the second analysis, patients were divided using to low time-averaged DAS28 (≤3.2) as the cut-off point. The survival distributions in both analyses were compared using log-rank testing. All analyses were performed using SPSS V.22.0.

RESULTS

There were 1157 patients included in the cohort. After exclusion of patients with a prior history of CVD, patients with a follow-up time <12 months or patients with two or less DAS28 measurements, 873 patients were included in the analyses. A total of 99 patients with RA developed a first CVD event during their first 10 years of follow-up: 44 (44%) cases of acute coronary syndrome (myocardial infarction or unstable angina pectoris), 18 (18%) cases of stable angina pectoris, 17 (17%) cases of CVA, 5 (5%) patients with a TIA, 10 (10%) cases of peripheral artery disease and 5 (5%) patients with heart failure. Out of all CVD events, 21% were fatal, mostly due to acute coronary syndrome (43%). Total follow-up time was 4560 patient years with a median (IQR) follow-up time of 5 (3–9) years. At baseline, there were differences between patients with and without CVD events (table 1). Patients with CVD events were on average older, and several other 'traditional' risk factors for CVD were raised including blood pressure, lipids and presence of diabetes. Patients who developed CVD were more frequently RF positive, not more frequently anti-CPP positive and had higher baseline disease activity (table 1). In total, 9151 DAS28 measurements were included during follow-up, and in 2738 (30%) of the visits, DAS28 was <2.6. Per patient, the percentage of their DAS28 measurements during follow-up that were scored <2.6 (time in remission) was in median (P25-P75) 17% (0.0–50%).

When disease activity was entered into the model as a continuous, segmented time-dependent variable, the results showed that disease activity had a significant effect on CVD risk after

Table 1 Patient characteristics at baseline

	Total cohort (n=873)	No CVD event (n=774)	CVD event (n=99)	p Value (CVD versus no CVD)
Age (years), mean±SD	54±14	53±14	62±9	<0.001
Sex (female), n (%)	574 (66)	524 (68)	50 (51)	0.001
Currently smoking, n (%)	272 (31)	235 (30)	69 (40)	0.156
BMI (weight(kg)/height (m²)), mean±SD	26±4	25±4	26±4	0.016
Systolic blood pressure (mm Hg), mean±SD	146±24	145±24	153±24	0.002
Diastolic blood pressure (mm Hg), mean±SD	84±12	83±12	86±11	0.026
Hypertension, n (%)	120 (14)	94 (12)	26 (26)	<0.001
Anti-hypertensives, n (%)	134 (15)	110 (14)	24 (24)	0.009
TC (mmol/L), mean±SD	5.2±1.2	5.2±1.2	5.3±1.4	0.448
HDL-c, mean±SD	1.3±0.3	1.3±0.3	1.2±0.3	0.040
TC:HDL-c ratio, mean±SD	4.1±1.0	4.1±1.0	4.4±1.0	0.013
LDL-c, mean±SD	3.2±1.1	3.1±1.0	3.2±1.2	0.357
Lipid lowering agents, n (%)	30 (3.4)	23(3)	7 (7)	0.035
Diabetes mellitus, n (%)	37 (4)	29 (4)	8 (8)	0.044
Family history of CVD, n (%)	265 (30)	232 (30)	33 (33)	0.494
Rheumatoid factor (positivity), n (%)	654 (75)	576 (74)	78 (79)	0.345
Anti-CCP (positivity), n (%)	554 (64)	493 (64)	61 (62)	0.686
DAS28, mean±SD	5.0±1.3	4.9±1.3	5.4±1.3	0.001
CRP, median (IQR)	14 (2-40)	13 (2-38)	21 (3-47)	0.083
HAQ, median (IQR)	0.6 (0.3–1.1)	0.6 (0.3–1.1)	0.7 (0.3–1.4)	0.468

Hypertension is defined as multiple measurements of elevated systolic blood pressure (>140 mm Hg) during multiple visits by a physician. Diabetes mellitus includes both type 1 and type 2. All variables represent baseline measures, except when otherwise stated.
anti-CCP, anti-cyclic citrullinated peptide; BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease; DAS28, 28-joint disease activity score; HAQ, Health Assessment Questionnaire; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TC, total cholesterol.

correction for confounders (table 2, panel B), indicating that CVD risk increases as DAS28 increases during follow-up. The HR, in table 2B, of 1.179 can be interpreted as an increase in risk of 18% if the DAS28 is one point higher. table 2, panel C, shows the results from the analysis with DAS28 ≤3.2 (yes/no) as a time-dependent variable after correction for confounders, indicating that CVD risk is significantly lower in patients with DAS28 ≤3.2 (HR 0.65, 95% CI 0.43 to 0.99).

The results from the Cox-proportional hazard analysis with remission (yes/no) as a time-dependent covariate showed a direction for a protective effect of time in remission against CVD (table 3, panel A and B) with an HR of 0.67. However, this effect did not reach statistical significance after correction for confounders (95% CI 0.43 to 1.07).

Mean±SD time-averaged DAS28 was 3.5±1.1 for the whole group, with a minimum and maximum time-averaged DAS28 of 0.7 and 7.3, respectively. The mean±SD time-averaged DAS28 was significantly lower in the non-event group compared with the event group (3.5±1.1 vs 3.9±1.2, respectively, with p<0.001). Results from a conventional Cox-proportional hazard regression analysis with time-averaged DAS28 as the main independent variable showed a significant effect on CVD with an HR of 1.60 (95% CI 1.28 to 1.99), as shown in table 4, panel B. After correction for confounders, the hazard of CVD notably increases with every point increase in time-averaged DAS28. The results from the following analysis (table 4, panel C) showed that, compared with patients with active disease, low time-averaged DAS28 (≤3.2) has a significant protective effect against CVD after correction for confounders (HR 0.53, 95% CI 0.34 to 0.84). Again a direction for a protective effect of time in remission against CVD was observed (not shown) with an HR of 0.78. However, this effect did not reach statistical significance after correction for confounders (95% CI 0.45 to 1.38). These results are in accordance with the results of the first set of analyses that included a time-dependent covariate.

For illustrative purposes, a Kaplan-Meier survival analysis was performed, investigating the effect of low disease activity and remission on time to first CVD event. Patients were divided into four groups; time-averaged DAS28 <2.6, 2.6–3.2, 3.2–5.1 and >5.1 for groups 1 through 4, respectively. Event rates were as follows: group 1 (n=189), 16 CVD events (8.5%); group 2 (n=163), 14 CVD events (8.6%); group 3 (n=444), 55 CVD events (12.4%) and group 4 (n=77), 14 CVD events (18%). Survival time (time to first CVD event) appears to decrease as time-averaged DAS28 increases (figure 1). Survival distributions differed significantly (p<0.027). Patients with the lowest survival rate (group 4) had the highest baseline DAS28 at diagnosis (mean±SD; 6.1±1.0) with 22% of patients diagnosed after the year 2000. The baseline DAS28 in groups 1, 2 and 3 was mean±SD: 4.1±1.3, 4.8±1.3 and 5.3±1.2, respectively. Of note, the survival distributions of patients with a time-averaged DAS28 <2.6 and a time-averaged DAS28 between 2.6 and 3.2 overlap indicating that these distributions do not differ significantly from each other. Figure 2 shows the survival distributions of patients with a time-averaged DAS28 ≤3.2 or very low disease activity over time and of patients with more active disease (time-averaged DAS28 >3.2). Survival distributions (figure 2) differed significantly (p=0.024).

DISCUSSION

Systemic inflammatory activity in RA has been suggested as an important contributing factor to the excess CVD risk in patients with RA. Therefore, it was hypothesised that achieving a state in which disease activity is low or nearly absent could have a beneficial effect on CVD risk. In this study, it is shown that low stable disease activity over time has a significant protective effect against CVD in RA. Although clinical remission (DAS28 <2.6) appears to have a protective effect against developing CVD, it did not reach statistical significance.

Table 2 Cox-proportional hazard regression analysis with time to first CVD event as the primary outcome and time-dependent DAS28 as the primary independent variable, before (panel A) and after (panel B) correction for confounders. Panel C shows results from the Cox-proportional hazards regression with DAS28 <3.2 (yes/no) as a time-dependent covariate after correction for confounders

				95% CI for Exp (B)	
	Beta	p Value	HR	Lower	Upper
Panel A: Crude model					
Time-dependent covariate (DAS28)	0.113	0.119	1.120	0.972	1.290
Age	0.064	<0.001	2.010	1.344	3.005
Gender	0.698	0.001	1.066	1.047	1.085
Panel B: Corrected model					
Time-dependent covariate (DAS28)	0.165	0.032	1.179	1.014	1.370
Age	0.062	<0.001	1.064	1.044	1.084
Gender	0.725	0.001	2.065	1.365	3.123
Hypertension baseline	1.036	<0.001	2.818	1.673	4.745
HDL-c	−0.736	0.043	0.466	0.222	0.977
CVD medication*	−0.515	0.026	0.597	0.379	0.940
DAS28 baseline	0.034	0.687	1.035	0.877	1.220
Panel C: Corrected model					
Time-dependent covariate (DAS28 <3.2)	−0.431	0.044	0.650	0.427	0.989
Age	0.064	<0.001	1.066	1.046	1.087
Gender	0.736	0.001	2.088	1.372	3.177
Hypertension	0.977	<0.001	2.656	1.547	4.559
HDL-c	−1.113	0.009	0.329	0.142	0.758
LDL-c	0.177	0.097	1.193	0.969	1.470
CVD medication*	−0.541	0.022	0.582	0.366	0.925
CRP	−0.001	0.538	0.999	0.994	1.003

*Anti-hypertensive medication, lipid lowering medication.
CRP, C-reactive protein; DAS28, 28-joint disease activity score; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.

Table 3 Cox-proportional hazard regression analysis with time to first CVD event as the primary outcome and remission as the time-dependent variable, before (panel A) and after (panel B) correction for confounders

				95% CI for Exp (B)	
	Beta	p Value	HR	Lower	Upper
Panel A: Crude model					
Time-dependent covariate (remission)	−0.211	0.358	0.810	0.516	1.270
Age	0.064	<0.001	1.066	1.047	1.086
Gender	0.665	0.001	1.945	1.304	2.901
Panel B: Corrected model					
Time-dependent covariate (remission)	−0.395	0.096	0.673	0.426	1.066
Age	0.063	<0.001	1.065	1.045	1.085
Gender	0.680	0.001	1.974	1.306	2.984
Hypertension	0.971	<0.001	2.640	1.540	4.528
HDL-c	−0.772	0.039	0.462	0.222	0.963
CVD medication*	−0.526	0.026	0.591	0.372	0.938

*Anti-hypertensive medication, lipid lowering medication.
CVD, cardiovascular disease; HDL-c, high-density lipoprotein cholesterol.

Previous studies demonstrated that inflammation contributes to accelerated atherosclerosis,[25–27] a cause of non-bleeding CVD. This study shows that active disease in RA is associated with an increased risk CVD. When looking at the overall trend of disease activity during follow-up, those patients who were able to achieve and maintain low disease activity over time appear to have a significantly lower risk of CVD than patients with more active disease. Interestingly, achieving remission did not offer any significant added value over sustained low disease activity, in terms of CVD risk reduction. Time to first CVD event was similar in patients with low disease activity and patients in remission and these patients had a significantly higher survival time compared with patients with more active disease. The results also showed that patients with the lowest survival times for CVD had the highest disease activity levels at baseline.

Several other studies have reported similar results with regard to increased disease activity in RA.[15 16 28 29] In another study, DAS28 did not appear to be significantly increased in patients with RA and myocardial infarction compared with RA controls.[29] However, only the first 6 months of follow-up after inclusion were incorporated for disease activity in this study. By contrast, Myasoedova *et al* have shown that particularly bouts of uncontrolled high disease activity are associated with a higher risk of CVD.[16] In another study that also included longitudinal disease activity, reduced time-averaged disease activity in RA was associated with fewer CVD events.[28] What our current study adds to that is notably longer follow-up with detailed data on determinants of CVD risk. Also, in this study, a Cox-proportional hazards regression with time-dependent covariates was used, as conventional Cox regression is potentially biassed.[30] Patients with RA in remission, defined as Clinical Disease Activity Index, or CDAI≤2.8, were found to have significantly lower levels of CVD risk markers compared with patients with active disease, supporting remission as a target for CVD risk management in RA.[17] Overall, patients who are able to achieve and maintain remission or low disease activity during follow-up, even sporadically, may be less likely to develop bouts of uncontrolled, sustained high systemic inflammation,

Table 4 Conventional Cox-proportional hazard regression analysis with time to first CVD event as the primary outcome and time-averaged DAS28 as the primary independent variable, before (panel A) and after (panel B) correction for confounders

				95% CI for Exp (B)	
	Beta	p Value	HR	Lower	Upper
Panel A: Crude model					
Time-averaged DAS28	0.383	<0.001	1.466	1.204	1.786
Age	0.060	<0.001	1.062	1.043	1.082
Gender	0.848	<0.001	2.336	1.549	3.521
Panel B: Full model					
Time-averaged DAS28	0.468	<0.000	1.597	1.279	1.994
Age	0.056	<0.001	1.057	1.037	1.077
Gender	0.954	<0.001	2.595	1.712	3.933
Hypertension baseline	0.920	<0.001	2.508	1.566	4.018
DAS28 baseline	−0.048	0.587	0.953	0.802	1.133
Panel D: Full model					
Time-averaged DAS28 binary; (≤3.2)	−0.630	0.007	0.533	0.337	0.843
Age	0.058	<0.001	1.060	1.040	1.080
Gender	0.803	<0.001	2.231	1.491	3.339
Hypertension baseline	0.882	<0.001	2.417	1.506	3.879
DAS28 baseline	0.042	0.614	1.043	0.886	1.228

DAS28, 28-joint disease activity score.

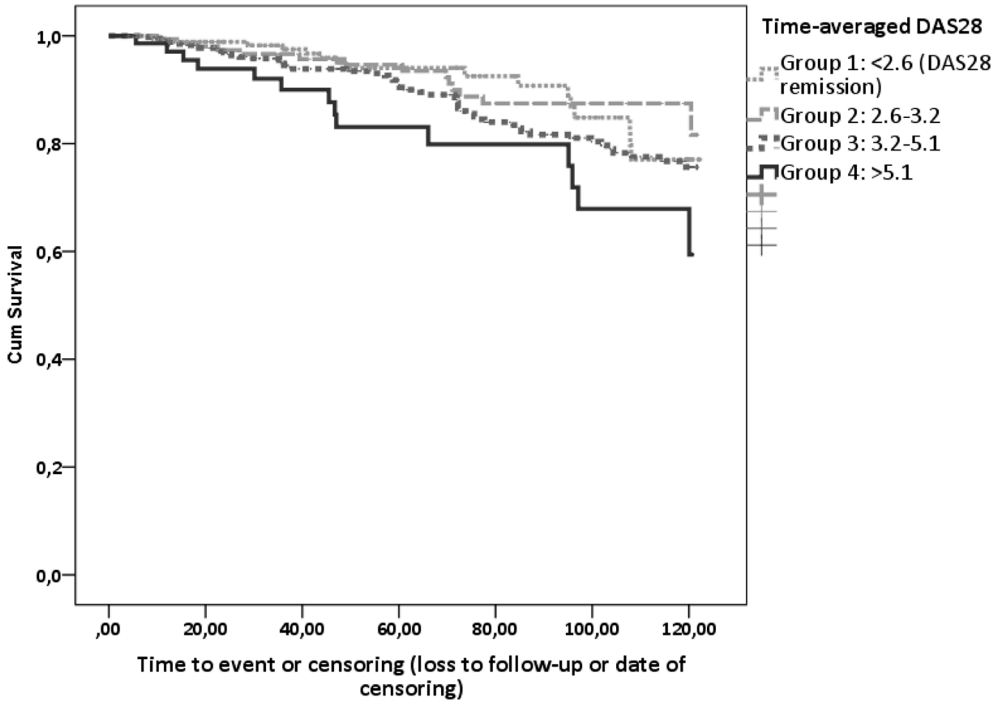

Figure 1 Survival distribution (time to first CVD event) for categories of time-averaged DAS28. Survival distributions differ significantly (p<0.027). Cumulative survival of CVD is depicted on the y-axis and time to a CVD event or censoring is depicted on the x-axis. CVD, cardiovascular disease; DAS28, 28-joint disease activity score.

a contributing factor to atherosclerosis and CVD. Patients with RA with very active disease at diagnosis, poor treatment response with more frequent flare-ups as a result, may form a subgroup within the RA population that is particularly at risk for developing CVD, significantly contributing to the excess CVD risk in this population.

Disease activity tends to fluctuate over the course for RA, which makes it difficult to accurately capture the level of exposure of a patient during follow-up. Also, as noted above, there may be a risk of bias as the patients who are able to stay event free the longest also have inherently more time to achieve remission or low disease activity, creating a

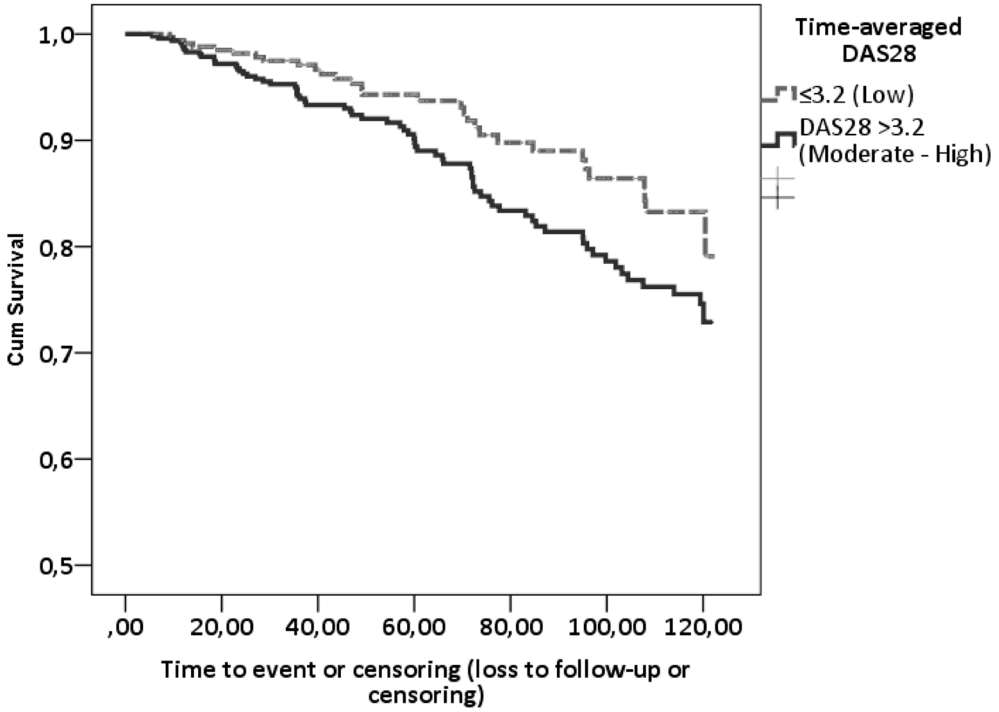

Figure 2 Survival distribution (time to first CVD event) for low (≤3.2) and moderate to high (>3.2) time-averaged DAS28. Survival distributions differ significantly (p<0.024). Cumulative survival of CVD is depicted on the y-axis and time to a CVD event or censoring is depicted on the x-axis. CVD, cardiovascular disease; DAS28, 28-joint disease activity score.

survivor bias or 'immortal time bias'. Immortal time bias can be avoided by integrating the changes in exposure status in the analysis.[30] Consequently, for this study, a Cox-proportional hazards regression with a segmented time-dependent covariate (DAS28) was chosen. For remission, there are a variety of definitions,[20 31–34] which were not all considered in this study. These definitions do appear to strongly correlate with each other;[32 33] however, including a different definition for remission could have an effect on results. DAS28 remission that was used in this study is defined as disease activity score <2.6 and this is not the same as the absolute absence of disease activity. On the other hand, remission according to the stricter ACR/EULAR remission criteria for RA is not prevalent, yet. Additional research in a larger cohort is needed to determine if clinical remission or the absence of inflammation has a significant added protective effect on CV risk compared with very low disease activity. Considering that the effect of low disease activity was found to be significant, it is likely that this effect is augmented for patients in remission. In a larger sample of patients, this effect may reach statistical significance. Finally, DMARDs were not included in study as it was hypothesised that DMARDs affect CVD risk through their effect on disease activity, the main independent variable in our analyses. Non-steroidal anti-inflammatory drugs may augment the risk of CVD. However, as they are often used intermittently, for short periods of time, while usage differs greatly between patients, accurately capturing the exposure is challenging. Determining their effect on CVD in RA may therefore be difficult. Also, not all NSAIDs may exert the same negative effect on the risk of CVD, complicating interpretation of results.[35]

In conclusion, this study shows that low DAS28 has a significant protective effect against the 10 year risk of CVD. Achieving sustained remission, here defined as DAS28 <2.6, is regarded as the ultimate treatment target and does not seem to provide a large advantage over low disease activity over time in terms further reducing CVD risk. Patients with RA with uncontrolled high disease activity appears to have the highest risk of developing CVD. Our results strengthen the use of tight control (treat-to-target) strategies in daily clinical practice to achieve low disease activity or remission in these patients, also with the aim to reduce CVD risk.

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Contributors All authors have given substantial contribution to the conception and design and/or analysis and interpretation of the data, have drafted and/or revised the manuscript critically for important intellectual content and have given final approval of the version to be submitted for publication. EEA 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 analysis.

Competing interests None delared.

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Notes