CHAPTER 7

Association with joint damage and physical functioning of nine composite indices and the 2011 ACR/EULAR remission criteria in rheumatoid arthritis

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ABSTRACT

Objective: To compare nine disease activity indices and the new American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) remission criteria in rheumatoid arthritis (RA) and to relate these to physical function and joint damage progression.

Methods: Five-year data from the BeSt study were used, a randomised clinical trial comparing four treatment strategies in 508 patients with recent-onset RA. Every three months disease activity was assessed with nine indices (Disease Activity Score (DAS), DAS-C reactive protein (DAS-CRP), Disease Activity Score in 28 joints (DAS28), DAS28-CRP, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) and three DAS versions with adjusted tender scores) and categorised into remission, low, moderate and high disease activity (LDA, MDA, HDA). In addition, ACR/EULAR clinical trial and practice remission was assessed 3-monthly with 28 and 68/66 joint counts. For each index, Generalized Estimating Equations analyses were performed to relate disease activity levels and the absence/presence of remission to 3-monthly assessments of physical functioning and annual radiological progression.

Results: From the composite indices, CDAI and SDAI were the most stringent definitions of remission and classified more patients as LDA. DAS28 and DAS28-CRP had the highest proportions of remission and MDA and a smaller proportion of LDA. ACR/EULAR remission percentages were comparable to CDAI/SDAI remission percentages. The variant including CRP and 68/66 joint counts was the most stringent. For all indices, higher levels of disease activity were associated with decreased functioning and more radiological damage progression. Despite differences in classification between the indices, no major differences in relation to the two outcomes were observed.

Conclusion: The associations of nine composite indices and ACR/EULAR remission criteria with functional status and joint damage progression showed high accordance, whereas the proportions of patients classified in the disease activity levels differed.

INTRODUCTION

Assessing disease activity and the response to treatment is of vital importance in rheumatoid arthritis (RA), both in clinical trials and in daily practice. By early and effective suppression of inflammation, severe joint destruction and functional disability can be prevented.[1,2] The use of a tightly controlled treatment approach, including frequent disease activity measurements and treatment towards a preset goal, have further improved outcomes.[3-6]

In order to measure disease activity, several composite scores have been developed such as the Disease Activity Score (DAS),[7] Disease Activity Score in 28 joints (DAS28),[8] the Clinical Disease Activity index (CDAI)[9] and the Simplified Disease Activity Index (SDAI)[10] as a combination of variables might represent actual disease activity better than single measures.[11] We recently validated three new variants of the original DAS with adjusted tender joint counts (TJCs).[12]

All composite scores on continuous scales can be subdivided into categories (remission, low disease activity (LDA), moderate disease activity (MDA) and high disease activity (HDA)), which nowadays are also being used as tools to guide treatment decisions for individual patients. Beside these index-based criteria, an international taskforce from the American College of Rheumatology (ACR) and the European League against Rheumatism (EULAR) recently developed new remission criteria for clinical practice and clinical trials.[13]

In previous studies the number of indices compared, patient numbers or duration of follow-up duration were limited and few studies related disease activity levels to functional ability or radiological damage progression in time. Little is known about the performance of the new ACR/EULAR remission criteria in comparison with existing index-based remission definitions.[14] To be able to compare the results of registries or clinical trials reliably using different composite scores, a more extended comparison is needed.

The aims of this study were: (1) to compare the classification of disease activity according to nine composite scores into remission, LDA, MDA and HDA; (2) to compare remission percentages of composite scores and the new ACR/EULAR remission criteria; and (3) to relate these levels of disease activity to physical functioning and progression of joint damage.

METHODS

Patients

Five-year follow-up data of the BeSt study were used in which 508 patients with recent-onset rheumatoid arthritis with a disease duration ≤2 years were randomised into four dynamic treatment strategies: 1) sequential monotherapy; 2) step-up combination therapy; 3) initial combination therapy with prednisone and 4) initial combination therapy with infliximab. Details have been described elsewhere.[15] Treatment was adjusted based on 3-monthly measurements of disease activity. If DAS was >2.4, the next step of the protocol was taken. If DAS was ≤2.4 for ≥6 months, the medication was tapered to monotherapy in a maintenance dose. From the third year the last dis-

ease-modifying antirheumatic drug (DMARD) could be tapered and discontinued if DAS was <1.6 for ≥6 months in patients on monotherapy at the maintenance dose. The last DMARD was restarted if DAS was ≥1.6.

Clinical assessments

Every three months the following variables were collected: 66 swollen joint count (SJC), 68 TJC, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), patient's assessment of global health (VAS-GH) on a visual analogue scale (0-100 mm) and physician's global assessment of disease activity (VAS-PGA)

At each timepoint disease activity was calculated according to the following composite indices *(table 1)*: the original DAS with ESR or CRP (DAS; DAS-CRP), DAS28 with ESR or CRP (DAS28; DAS28-CRP), SDAI, CDAI, and three variants of the original DAS with adjustments in the TJC of the score.[12] In the first adjustment (DAS 0-1) the same joints and joint groups were used as in the Ritchie Articular Index (RAI) but scoring only absence (0) or presence (1) of tenderness instead of grading tenderness from 0 to 3. In the second adjusted version (DAS-TJC53), grading and assessment of joint groups were omitted: all 53 joints of the RAI counted separately for the absence or presence of tenderness. In the last version only the 44 joints (equal to the joints assessed for swelling) were assessed for the absence or presence of tenderness (DAS-TJC44). Furthermore, the presence or absence of ACR/EULAR remission was assessed using the following components: SJC ≤1, TJC ≤1, VAS global health ≤1 cm and CRP ≤1 g/dl. Four variants were used: a clinical trial definition including CRP and a clinical practice definition excluding CRP, each with a 28/28 SJC/TJC and with a 68/66 SJC/TJC.

At each time point patients were classified as being in remission (yes/no) according to nine composite indices and ACR/EULAR remission criteria, or in LDA, MDA or HDA according to nine composite indices based on previously published cut-off points *(table 1)*.[16–20] For the three simplifications of the original DAS, the cut-off points of the original DAS were used.

Outcome assessments

Every 3 months functional capacity was assessed using the health assessment questionnaire (HAQ).[21] Joint damage was assessed on annual x-rays from baseline until year 5 per patient in random order using the Sharp-van der Heijde method[22] by two independent readers blinded to patient identity. The mean scores of the two readers were used.

Statistical analysis

SPSS Version 17.0 was used for all analyses. To assess the relationship between the level of disease activity according to the nine disease activity indices, ACR/EULAR remission criteria and HAQ, four Generalised Estimating Equations (GEE) analyses were performed per index, first with HAQ per patient as a continuous outcome and with HAQ per patient as a dichotomous outcome for three cut-off points (HAQ >1.0, HAQ >0.5, HAQ >0).

The disease activity level was added as an explanatory variable categorised as remission,

TABLE 1 Overview of composite indices

	Formula	Remission	LDA	MDA	HDA
DAS	0.5398√(RAI) + 0.06465(SJC44) + 0.330ln(ESR) + 0.00722($VAS_{patient}$ [mm])	<1.6	≥1.6 and ≤2.4	>2.4 and ≤3.7	>3.7
DAS CRP	0.54√(RAI) + 0.065(SJC44) + 0.17ln(CRP[mg/l]+1) + 0.0072($VAS_{patient}$ [mm]) + 0.45	<1.6	≥1.6 and ≤2.4	>2.4 and ≤3.7	>3.7
DAS28	0.56√(TJC28) + 0.28√(SJC28) + 0.70ln(ESR) + 0.014($VAS_{patient}$ [mm])	<2.6	≥2.6 and ≤3.2	>3.2 and ≤5.1	>5.1
DAS28 CRP	0.56√(TJC28) + 0.28√(SJC28) + 0.36ln(CRP[mg/l]+1) + 0.014($VAS_{patient}$ [mm]) + 0.96	<2.6	≥2.6 and ≤3.2	>3.2 and ≤5.1	>5.1
SDAI	TJC28 + SJC28 + $VAS_{physician}$ (cm) + $VAS_{patient}$ (cm) + CRP (mg/dl)	≤3.3	>3.3 and ≤11	>11 and ≤26	>26
CDAI	TJC28 + SJC28 + $VAS_{physician}$ (cm) + $VAS_{patient}$ (cm)	≤2.8	>2.8 and ≤10	>10 and ≤22	>22
DAS 0-1	0.5398√(RAI_wg) + 0.06465(SJC44) + 0.330ln(ESR) + 0.00722($VAS_{patient}$ [mm])	<1.6	≥1.6 and ≤2.4	>2.4 and ≤3.7	>3.7
DAS TJC_{53}	0.5398√(TJC_{53}) + 0.06465(SJC44) + 0.330ln(ESR) + 0.00722($VAS_{patient}$ [mm])	<1.6	≥1.6 and ≤2.4	>2.4 and ≤3.7	>3.7
DAS TJC_{44}	0.5398√(TJC_{44}) + 0.06465(SJC44) + 0.330ln(ESR) + 0.00722($VAS_{patient}$ [mm])	<1.6	≥1.6 and ≤2.4	>2.4 and ≤3.7	>3.7

LDA, low disease activity; MDA, moderate disease activity; HDA, high disease activity; DAS, disease activity score; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DAS28, disease activity score in 28 joints, SDAI, simplified disease activity index; CDAI, clinical disease activity index; DAS 0-1, disease activity score with 'Ritchie articular index' without grading; TJC_{53}, tender joint count in 53 joints; TJC_{44}, tender joint count in 44 joints RAI, ritchie articular index; SJC_{44}, swollen joint count in 44 joints; $VAS_{patient}$, patient's assessment of global health on a visual analogue scale; TJC_{28}, tender joint count in 28 joints; SJC_{28}, swollen joint count 28 joints; $VAS_{physician}$, physician's assessment of disease activity on a visual analogue scale.

LDA, MDA and HDA, or as remission yes/no. All analyses were corrected for baseline HAQ, time, age, gender and treatment group with additional correction for time*time in the continuous HAQ analysis to approach linearity. For each disease activity level (remission, LDA, MDA, HDA or remission yes/no) and per composite score the mean HAQ scores (continuous outcome) and probabilities of an HAQ score above the cut-off point (dichotomous outcome) were estimated within the GEE model. For this purpose the Estimated Marginal Means subcommand was used which fills in the regression equation by fixing continuous values of covariates at their means and estimates HAQ values for each level of a categorical variable. This option was used to avoid differences in distribution of confounders between different disease activity levels and composite scores.

To assess the relationship between the level of disease activity according to the different composite indices, ACR/EULAR remission and the progression of joint damage, four GEE analyses were performed for each composite index: first with the absolute annual Sharp-van der Heijde progression score (SHS) progression per year as a continuous outcome and then with the annual SHS progression as a dichotomous outcome (cut-off points ≥1, ≥3 and ≥5 SHS units progression per year). Since x-rays were taken annually and disease activity was measured every three months, for the analysis including composite scores only the mean disease activity per year was calculated by the following formula: (0.5*DAS_1 + DAS_2 + DAS_3 + DAS_4 + 0.5*DAS_5)/4 and categorised into remission, LDA, MDA and HDA. For single missing values we used a last observation carried forward method before calculating mean disease activity per year. This categorical mean

disease activity level per year or remission yes/no was added as an explanatory variable. Remission per year was defined as ≥3/4 visits remission.
The SHS analyses were corrected for total SHS at the beginning of each year, time, presence of cyclic citrullinated peptides (CCP) antibodies, treatment group, age and gender. Mean progression scores and probabilities for progression were estimated for index and each disease activity level using estimated marginal means.
The GEE method with M-dependence covariance structure was used to correct for within-patient correlation since HAQ and joint damage progression was repeated measured over time.

RESULTS

At baseline, patients (n=508) had active disease with a mean (SD) DAS of 4.4 (0.9) and a mean (SD) HAQ of 1.4 (0.9). Mean (SD) / median (IQR) SHS at baseline was 7.1 (10.2) / 3.0 (0.5 – 9.5).

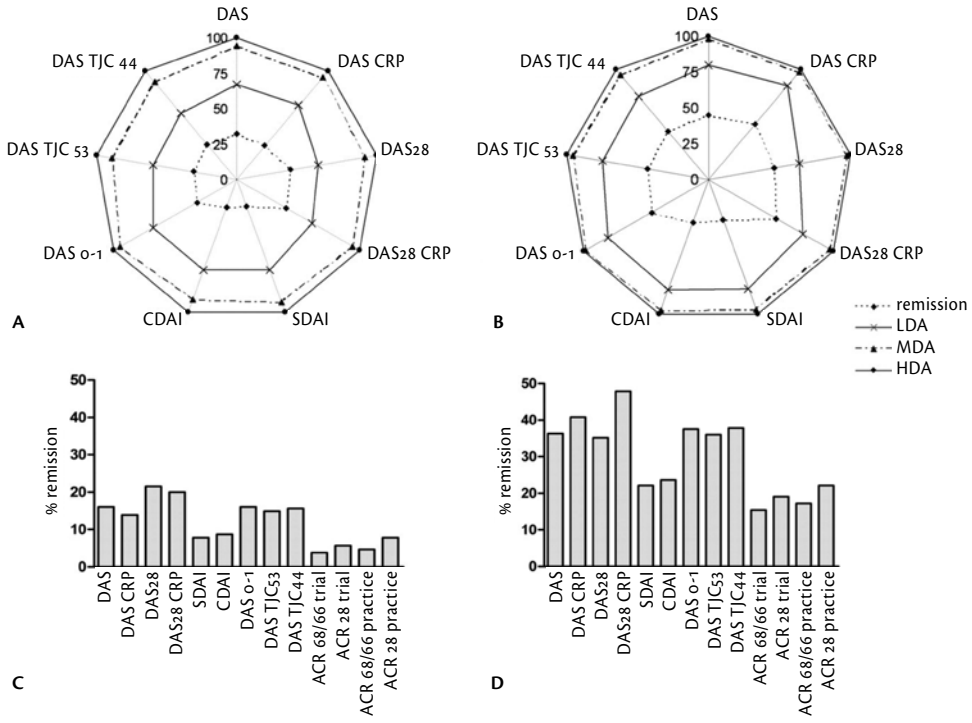

FIGURE 1 Spider diagrams showing the cumulative percentage of patients in remission, low, moderate and high disease activity according to the different composite indices at (A) 1 year (n=415) and (B) 5 year (n=317). Bar charts show the percentage of patients in remission (≥3 visits) during (C) year 1 (n=424) and (D) year 5 (n=267) per remission definition. ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; DAS 0-1, Disease Activity Score with RAI 0-1; DAS28, Disease Activity Score in 28 joints; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity; SDAI, Simplified Disease Activity Index; TJC, tender joint count.

TABLE 2 Mean predicted HAQ for patients in remission, LDA, MDA and HDA. Covariates and factors appearing in the model are fixed at the following values: baseline HAQ 1.4; visit 10.6; age 53.9; treatment group 1; female gender.

	Remission	LDA	MDA	HDA
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
DAS	0.48 (0.40 – 0.55)	0.61 (0.53 – 0.69)	0.83 (0.75 – 0.91)	1.24 (1.14 – 1.33)
DAS CRP	0.49 (0.41 – 0.57)	0.63 (0.55 – 0.71)	0.87 (0.79 – 0.95)	1.27 (1.17 – 1.38)
DAS28	0.49 (0.41 – 0.57)	0.60 (0.52 – 0.68)	0.76 (0.67 – 0.84)	1.20 (1.10 – 1.29)
DAS28 CRP	0.52 (0.44 – 0.60)	0.62 (0.54 – 0.70)	0.80(0.72 – 0.89)	1.28 (1.18 – 1.38)
SDAI	0.47 (0.39 – 0.55)	0.60 (0.52 – 0.68)	0.83 (0.75 – 0.92)	1.24 (1.14 – 1.33)
CDAI	0.46 (0.38 – 0.54)	0.60 (0.52 – 0.68)	0.83 (0.74 – 0.91)	1.18 (1.09 – 1.28)
DAS 0-1	0.48 (0.40 – 0.56)	0.61 (0.53 – 0.70)	0.84 (0.76 – 0.92)	1.26 (1.16 – 1.36)
DAS TJC53	0.47 (0.39 – 0.55)	0.60 (0.52 – 0.68)	0.77 (0.69 – 0.85)	1.13 (1.03 – 1.22)
DAS TJC44	0.48 (0.40 – 0.56)	0.60 (0.52 – 0.68)	0.78 (0.70 – 0.86)	1.14 (1.05 – 1.24)

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; DAS 0-1, Disease Activity Score with RAI 0-1; DAS28, Disease Activity Score in 28 joints, HAQ, Health Assessment Questionnaire; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity; SDAI, Simplified Disease Activity Index; TJC44, tender joint count 44 joints; TJC53, tender joint count 53 joints.

Spider diagrams

Spider diagrams *(figure 1 A,B)* illustrate the classification in disease activity categories according to the different composite indices. Irrespective of the composite score used, more patients were classified in HDA categories in year 1 than in year 5, reflecting treatment efficacy. From the composite indices, CDAI and SDAI had the most stringent definitions of remission and thus classified a relatively high proportion of patients in the LDA category. The proportions of patients in MDA and HDA were comparable between CDAI, SDAI, DAS and DAS-CRP. DAS28 and DAS28-CRP had the highest proportions remission and MDA and a relatively small proportion of patients in LDA. Of the adjusted DAS versions, DAS 0-1 was very comparable with the original DAS. The absolute DAS-TJC53 and, to a lesser extent, the DAS-TJC44 were slightly higher than the original DAS, resulting in higher percentages of patients in the HDA. *Figure 1 C,D* show the remission percentages of the composite indices and ACR/EULAR remission criteria. The most stringent definition is the clinical trial definition with 66/68 joints. Clinical trial remission criteria showed lower remission percentages than clinical practice remission criteria, as did the criteria including a full 68/66 joint count compared with the criteria based on 28-joint counts.

Relation with functional ability

In general, predicted HAQ values among the disease activity levels based on the composite indices showed high agreement *(table 2)*. As expected, HAQ values are lower when the level of disease activity was lower. Although CDAI and SDAI classified fewer patients as being in remission, CDAI and SDAI remission was not associated with lower HAQ scores than other indices *(table 2)*. Compared with other indices, DAS28 variants classified the highest proportion of patients in the remission and MDA categories, and fewer patients in LDA category, but HAQ levels in remission, LDA and MDA were com-

TABLE 3 Estimated probability for HAQ scores >0.5 in patients in remission, LDA, MDA and HDA Covariates and factors appearing in the model are fixed at the following values: baseline HAQ 1.4; visit 10.6; age 53.9; treatment group 1; female gender.

	Remission	LDA	MDA	HDA
	Probability (95% CI)	Probability (95% CI)	Probability (95% CI)	Probability (95% CI)
DAS	0.34 (0.27 – 0.40)	0.49 (0.42 – 0.57)	0.69 (0.63 – 0.75)	0.90 (0.86 – 0.93)
DAS CRP	0.34 (0.27 – 0.41)	0.52 (0.44 – 0.59)	0.73 (0.67 – 0.79)	0.90 (0.85 – 0.94)
DAS28	0.36 (0.29 – 0.43)	0.48 (0.40 – 0.55)	0.63 (0.56 – 0.70)	0.87 (0.83 – 0.92)
DAS28 CRP	0.39 (0.32 – 0.46)	0.51 (0.44 – 0.58)	0.68 (0.62 – 0.75)	0.90 (0.86 – 0.94)
SDAI	0.31 (0.25 – 0.38)	0.47 (0.40 – 0.55)	0.70 (0.63 – 0.76)	0.86 (0.81 – 0.91)
CDAI	0.31 (0.25 – 0.38)	0.47 (0.39 – 0.54)	0.70 (0.64 – 0.76)	0.85 (0.80 – 0.89)
DAS 0-1	0.34 (0.27 – 0.41)	0.50 (0.43 – 0.58)	0.70 (0.64 – 0.76)	0.91 (0.88 – 0.95)
DAS TJC53	0.34 (0.28 – 0.41)	0.49 (0.42 – 0.56)	0.65 (0.59 – 0.72)	0.85 (0.80 – 0.89)
DAS TJC44	0.35 (0.28 – 0.41)	0.49 (0.41 – 0.56)	0.66 (0.59 – 0.72)	0.85 (0.81 – 0.90)

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; DAS 0-1, Disease Activity Score with RAI 0-1; DAS28, Disease Activity Score in 28 joints, HAQ, Health Assessment Questionnaire; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity; SDAI, Simplified Disease Activity Index; TJC44, tender joint count 44 joints; TJC53, tender joint count 53 joints.

parable to other indices. Patients in HDA according to the DAS-TJC53 and DAS-TJC44 have lower HAQ scores than patients in HDA according to other indices.
Similar results were seen with regard to the probability of a HAQ score >0.5 as outcome (*table 3*). Overall, 34-91% of patients were limited in functioning depending on their disease activity level. HDA corresponds with a higher chance of functional limitations. In general there was little difference between the percentages of HAQ scores >0.5 for all composite scores, but the same subtle differences were found as were seen previously. In the analysis including ACR/EULAR remission definitions, the same pattern was found (*table 6*). Predicted HAQ scores and probabilities for a HAQ score >0.5 were comparable for all definitions, with SDAI, CDAI and ACR/EULAR remission at the lower end of range. Very little difference was found within the group of ACR/EULAR remission definitions.

Relation to the progression of joint damage

Table 4 shows predicted values of SHS progression for patients in different disease activity levels according to the nine indices. All indices showed similar joint damage progression in different disease activity levels, and all composite indices showed a dose response with a higher level of disease activity levels yielding more joint damage progression. Although CDAI and SDAI classified fewer patients as being in remission, CDAI and SDAI remission were not associated with less damage progression. In the HDA category, patients with DAS-TJC53 an DAS-TJC44 had somewhat less SHS progression than patients in HDA according to other indices (*table 4*).
Predicted probabilities for SHS progression ≥3 units for patients in remission, LDA, MDA and HDA categories according to the nine indices are shown in *table 5*. The proportions of SHS progression between different composite indices were very comparable. The percentage of CCP-positive female patients in remission showing joint damage progression

TABLE 4 Mean predicted Δ SHS for patients in remission, LDA, MDA and HDA. Covariates and factors appearing in the model are fixed at the following values: previous SHS 10.3; year 2.8; age 53.8; treatment group 1; anti-CCP positive patients; female gender.

	Remission	LDA	MDA	HDA
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
DAS	3.5 (-0.1 – 7.0)	5.5 (2.4 – 8.7)	7.3 (4.1 – 10.6)	11.7 (7.4 – 16.0)
DAS CRP	4.1 (1.0 – 7.2)	5.4 (2.3 – 8.6)	6.7 (3.6 – 9.8)	11.7 (7.1 – 16.4)
DAS28	3.6 (0.1 – 7.0)	4.6 (1.4 – 7.8)	6.9 (3.8 – 10.0)	10.8 (6.8 – 14.8)
DAS28 CRP	3.5 (0.0 – 7.1)	5.5 (2.3 – 8.7)	8.1 (4.8 – 11.3)	13.2 (8.5 – 17.8)
SDAI	4.0 (0.8 – 7.3)	4.7 (1.4 – 8.0)	7.4 (4.2 – 10.6)	11.5 (7.3 – 15.7)
CDAI	3.9 (0.6 – 7.1)	4.7 (1.4 – 7.9)	7.4 (4.2 – 10.6)	11.0 (6.9 – 15.0)
DAS 0-1	3.4 (-0.1 – 6.9)	5.5 (2.3 – 8.6)	7.2 (4.0 – 10.4)	12.7 (8.2 – 17.1)
DAS TJC53	3.5 (0.2 – 6.9)	4.8 (1.5 – 8.1)	6.9 (3.7 – 10.1)	9.9 (6.0 – 13.8)
DAS TJC44	3.6 (0.3 – 7.0)	4.9 (1.6 – 8.2)	7.2 (4.0 – 10.4)	10.2 (6.3 – 14.2)

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; DAS 0-1, Disease Activity Score with RAI 0-1; DAS28, Disease Activity Score in 28 joints; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity; SDAI, Simplified Disease Activity Index; SHS, Sharp-van der Heijde score; TJC44, tender joint count 44 joints; TJC53, tender joint count 53 joints

TABLE 5 Estimated probability (95% CI) for SHS progression ≥3 units in patients in remission, LDA, MDA and HDA. Covariates and factors appearing in the model are fixed at the following values: previous SHS 10.3; year 2.8; age 53.8; treatment group 1; anti-CCP positive patients; female gender.

	Remission	LDA	MDA	HDA
	Probability (95% CI)	Probability (95% CI)	Probability (95% CI)	Probability (95% CI)
DAS	0.10 (0.06 – 0.15)	0.18 (0.12 – 0.25)	0.31 (0.21 – 0.40)	0.59 (0.44 – 0.74)
DAS CRP	0.12 (0.07 – 0.18)	0.19 (0.13 – 0.26)	0.33 (0.23 – 0.43)	0.61 (0.46 – 0.76)
DAS28	0.09 (0.05 – 0.14)	0.14 (0.08 – 0.20)	0.27 (0.19 – 0.35)	0.55 (0.40 – 0.69)
DAS28 CRP	0.10 (0.06 – 0.15)	0.18 (0.12 – 0.24)	0.34 (0.24 – 0.43)	0.66 (0.49 – 0.82)
SDAI	0.09 (0.03 – 0.14)	0.15 (0.10 – 0.20)	0.32 (0.23 – 0.41)	0.54 (0.40 – 0.68)
CDAI	0.09 (0.04 – 0.15)	0.15 (0.10 – 0.21)	0.34 (0.25 – 0.44)	0.50 (0.37 – 0.63)
DAS 0-1	0.10 (0.05 – 0.15)	0.19 (0.12 – 0.25)	0.31 (0.22 – 0.40)	0.66 (0.51 – 0.81)
DAS TJC53	0.10 (0.05 – 0.14)	0.17 (0.11 – 0.23)	0.29 (0.20 – 0.38)	0.46 (0.34 – 0.58)
DAS TJC44	0.09 (0.05 – 0.14)	0.18 (0.12 – 0.24)	0.31 (0.22 – 0.40)	0.47 (0.35 – 0.60)

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; DAS 0-1, Disease Activity Score with RAI 0-1; DAS28, Disease Activity Score in 28 joints; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity; SDAI, Simplified Disease Activity Index; SHS, Sharp-van der Heijde score; TJC44, tender joint count 44 joints; TJC53, tender joint count 53 joints.

varies between 9% and 12% for progression of ≥3 (*table 5*). The chance of progression ≥3 units in CCP-negative patients in remission was lower (3-4% SHS progression ≥3 units, data not shown). Patients in SDAI and CDAI remission had comparable chances of progression of ≥3 units as other indices (9% vs 9-12%). The probability for progression of ≥3 units in the LDA category was slightly lower with SDAI, CDAI and DAS28 than with other indices. The four versions of the ACR/EULAR remission criteria were comparably related to joint damage progression (*table 6*). The probability of annual SHS progression of ≥3 units for patients in remission was 9-12% compared with 24-28% for patients not

in remission. Probabilities for progression as well as absolute SHS progression values were comparable for all definitions. Comparable patterns were seen for annual SHS progression of ≥1 and ≥5 units (data not shown).

DISCUSSION

We compared classification into remission, LDA, MDA and HDA or remission yes/no with nine composite disease activity scores and ACR/EULAR remission criteria and assessed the relationship with functional ability and radiological damage progression. Although the proportions of patients classified varied between some of disease activity levels and definitions, the associations of all composite scores and remission definitions with HAQ and SHS showed overall high agreement. All showed a good dose-response relationship of disease activity with HAQ and SHS progression.

This analysis expands on earlier studies comparing composite indices. We compared composite scores including 28-joint counts and also the original DAS and several adjustments. Previous studies showed that DAS28 classifies more patients in remission,[23-26] while SDAI and CDAI are more strict in classifying remission[23,27] as reflected by lower remission percentages, which is in line with our results. In general, the studies that link composite scores to functional ability and radiological progression show that DAS28, SDAI and CDAI correlate comparable with HAQ and Larsen scores. They demonstrate that levels of disease activity of these indices discriminate between levels of functional state and radiological damage.[9,17,28,29] We showed that all nine composite indices had a comparable relationship with radiological joint damage or physical functioning. Omitting grading in TJCs and/or omitting scoring tender joints in joint groups did not change this relationship. The same is true if acute phase reactants are left out (CDAI and clinical trial ACR/EULAR remission criteria).

Which index should be preferred will depend on the reason for using the index and on personal preferences. In clinical practice, composite scores without an acute phase reactant or a limited joint count can be used whereas, in a clinical trial setting, a more elaborate composite score can be valuable. If treatment is aimed at remission, strict remission criteria carry a higher risk of overtreatment. However, a less strict definition may lead to residual disease activity and thereby undertreatment. SDAI, CDAI and ACR/EULAR remission criteria classified the lowest proportion of patients in remission than the other indices but were not associated with lower HAQ scores and did not lead to clinically significant less joint damage progression. DAS28 and DAS28-CRP classified the highest proportion of patients in clinical remission without compromising on HAQ and joint damage progression. However, within these indices patients' feet are not examined, which may not be appreciated. If LDA should be the target, DAS28 variants may be less useful because DAS28 and DAS28-CRP classified fewer patients in LDA and remission together than other indices without leading to better HAQ and less joint damage progression.

Our results emphasise earlier reports that clinical remission does not necessarily coincide with radiological remission.[30-32] The predicted probability for joint damage progression (≥3 units) was 9-12% in anti-CCP-positive patients. This suggests that there is (sub) clinical inflammation in patients in clinical remission, even with stricter definitions. An additional explanation might be that there is a delay between inflammation measured with clinical parameters and progression of joint damage visible on conventional x-rays. Part of the joint damage progression seen in patients in clinical remission might reflect disease activity that was present before the onset of clinical remission.[33] Our results emphasise that a comprehensive definition of disease remission needs to include radiological outcome.

TABLE 6 Estimated mean predicted HAQ scores and mean SHS progression scores and estimated probability for HAQ scores >0.5 and SHS progression ≥3 units in patients in remission versus no remission. Covariates and factors appearing in the HAQ model are fixed at the following values: baseline HAQ 1.4; visit 10.6; age 53.9; treatment group 1; female gender. Covariates and factors appearing in the SHS model are fixed at the following values: previous SHS 10.3; year 2.8; age 53.8; treatment group 1; anti-CCP positive patients; female gender

	HAQ >0.5		Absolute HAQ value		SHS ≥3.0		Absolute SHS value	
	Remission	No remission	Remission	No remission	Remission	No remission	Remission	No remission
	Probability (95% CI)	Probability (95% CI)	Mean (95% CI)	Mean (95% CI)	Probability (95% CI)	Probability (95% CI)	Mean (95% CI)	Mean (95% CI)
DAS	0.39 (0.32 – 0.45)	0.62 (0.55 – 0.68)	0.52 (0.44 – 0.60)	0.73 (0.64 – 0.82)	0.11 (0.06 – 0.16)	0.27 (0.20 – 0.33)	4.8 (1.3 – 8.3)	6.5 (3.0 – 10.0)
DAS CRP	0.38 (0.32 – 0.45)	0.63 (0.56 – 0.69)	0.52 (0.44 – 0.61)	0.74 (0.65 – 0.82)	0.12 (0.07 – 0.17)	0.27 (0.21 – 0.34)	5.2 (1.6 – 8.8)	6.5 (3.0 – 10.1)
DAS28	0.39 (0.32 – 0.46)	0.60 (0.53 – 0.67)	0.52 (0.43 – 0.61)	0.73 (0.64 – 0.82)	0.11 (0.06 – 0.15)	0.26 (0.20 – 0.33)	4.6 (1.1 – 8.1)	6.6 (3.3 – 10.2)
DAS28 CRP	0.41 (0.34 – 0.48)	0.63 (0.57 – 0.70)	0.54 (0.46 – 0.63)	0.75 (0.67 – 0.84)	0.12 (0.07 – 0.17)	0.28 (0.21 – 0.35)	5.2 (1.7 – 8.7)	6.7 (3.2 – 10.3)
SDAI	0.36 (0.30 – 0.43)	0.58 (0.51 – 0.65)	0.51 (0.42 – 0.59)	0.70 (0.61 – 0.79)	0.11 (0.04 – 0.17)	0.24 (0.18 – 0.31)	5.6 (2.2 – 9.0)	6.3 (2.7 – 9.9)
CDAI	0.37 (0.30 – 0.43)	0.58 (0.52 – 0.65)	0.50 (0.42 – 0.59)	0.70 (0.61 – 0.79)	0.09 (0.03 – 0.14)	0.25 (0.18 – 0.31)	5.3 (1.9 – 8.8)	6.3 (2.7 – 9.9)
DAS 0-1	0.39 (0.32 – 0.45)	0.62 (0.55 – 0.68)	0.52 (0.44 – 0.60)	0.73 (0.64 – 0.82)	0.11 (0.06 – 0.16)	0.27 (0.20 – 0.34)	4.8 (1.3 – 8.3)	6.5 (3.0 – 10.0)
DAS TJC53	0.39 (0.33 – 0.46)	0.61 (0.55 – 0.68)	0.52 (0.44 – 0.60)	0.73 (0.64 – 0.81)	0.12 (0.07 – 0.17)	0.26 (0.20 – 0.33)	4.8 (1.3 – 8.3)	6.5 (3.0 – 10.0)
DAS TJC44	0.40 (0.33 – 0.46)	0.61 (0.55 – 0.68)	0.53 (0.44 – 0.61)	0.73 (0.64 – 0.81)	0.12 (0.07 – 0.17)	0.26 (0.20 – 0.33)	4.7 (1.2 – 8.2)	6.5 (3.0 – 10.0)
ACR 68/66 trial	0.35 (0.28 – 0.41)	0.56 (0.49 – 0.63)	0.52 (0.43 – 0.60)	0.68 (0.59 – 0.76)	0.09 (0.02 – 0.15)	0.24 (0.18 – 0.30)	5.1 (1.4 – 8.7)	6.3 (2.7 – 9.8)
ACR 28 trial	0.34 (0.28 – 0.41)	0.57 (0.50 – 0.63)	0.51 (0.42 – 0.59)	0.69 (0.60 – 0.77)	0.10 (0.04 – 0.17)	0.24 (0.18 – 0.30)	5.2 (1.7 – 8.8)	6.3 (2.7 – 9.9)
ACR 68/66 practice	0.35 (0.28 – 0.41)	0.57 (0.50 – 0.64)	0.51 (0.42 – 0.60)	0.68 (0.60 – 0.77)	0.09 (0.03 – 0.15)	0.24 (0.18 – 0.30)	5.0 (1.3 – 8.6)	6.4 (2.8 – 10.0)
ACR 28 practice	0.35 (0.28 – 0.41)	0.58 (0.51 – 0.65)	0.50 (0.41 – 0.59)	0.69 (0.61 – 0.78)	0.11 (0.05 – 0.16)	0.25 (0.18 – 0.31)	5.2 (1.6 – 8.8)	6.4 (2.8 – 10.0)

ACR, American College of Rheumatology; CCP, cyclic citrullinated peptide; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS, Disease Activity Score; DAS 0-1, Disease Activity Score with RAI 0-1; DAS28, Disease Activity Score in 28 joints; SDAI, Simplified Disease Activity Index; SHS, Sharp-van der Heijde score; TJC44, tender joint count 44 joints; TJC53, tender joint count 53 joints.
ACR 68/66 trial: ACR/EULAR remission definition for clinical trials including a 68/66 joint count; ACR 28 trial: ACR/EULAR remission definition for clinical trials including a 28 joint count; ACR 68/66 practice: ACR/EULAR remission definition for clinical practice including a 68/66 joint count; ACR 28 practice: ACR/EULAR remission definition for clinical practice including a 28 joint count

Previous studies have shown that, early in the disease course active inflammation (reflected in composite indices) is the main determinant of functional limitations while, in more established disease, joint damage becomes more important.[1,34,35] We analysed the association between disease activity levels and HAQ in patients with limited joint damage during a 5-year follow-up period. In more advanced disease the dose response between disease activity levels and HAQ is probably less pronounced and/or HAQ values among remission patients may be higher.

There is a large body of evidence supporting the benefit of targeted treatment. Less is known on what the target should be.[5,36] RCTs directly comparing LDA and remission as targets are lacking. In the BeSt study treatment was aimed at LDA. There is little difference between the mean HAQ in LDA (~0.60) and in remission (~0.50). However, progression rates in patients in LDA are considerably higher than those patients in remission, suggesting that treatment should aim at remission. It is not known what the gain would be on clinical and radiological outcomes while risking higher turnover in treatment options.

When outcomes are dichotomised, only part of the data is being used, in contrast to using data on a continuous scale. Joint damage progression, (and, to a lesser extent HAQ) does not follow a Gaussian distribution. Although the GEE method is relatively robust against violations of the normal distribution, it is impossible to disentangle the complete effect of the distribution on continuous outcomes and predicted means. This may explain part of the high predicted annual progression rate, which can also be explained by unfavourable characteristics like anti-CCP positivity and treatment group. With dichotomous outcomes, the distribution is not a problem. Therefore we decided to show both.

The strengths of our study are that we compared the most widely used composite indices for RA and recently published ACR/EULAR remission criteria with different joint counts and related the classification of these indices to HAQ and joint damage progression (SHS) in a large group of patients. Also, all indices/criteria were repeatedly measured over time, increasing the number of observations, and were incorporated in the GEE analyses. One limitation might be that 'old' ACR remission criteria were not included in the analyses as not all components of these criteria were gathered 3-monthly.

In conclusion, although there are differences in classification between 9 different disease activity composite indices and ACR/EULAR remission definitions for RA, the associations with functional status and joint damage progression are highly comparable. The choice of composite index is dependent on its intended use.

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