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# Remission *vs* low disease activity: function, quality of life and structural outcomes in the Early Rheumatoid Arthritis Study and Network

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## Abstract

**Objectives.** To examine associations between function, quality of life and structural outcomes in patients achieving remission *vs* low disease activity in early RA.

**Methods.** Demographic, clinical and radiographic variables were collected at baseline and then annually from the Early Rheumatoid Arthritis Study (ERAS) and Early Rheumatoid Arthritis Network (ERAN) inception cohorts in routine care from 1986 to 2012. Disease activity was categorized: mean DAS28 score between years 1 and 5: remission [mean remission DAS (mRDAS) <2.6] or low [mean low DAS (mLDAS) 2.6–3.2]; sustained low/remission DAS28 (sLDAS/sRDAS) at years 1 and 2; and sustained Boolean remission (sBR) at years 1 and 2. Changes in HAQ and Short Form 36 Health Survey Questionnaire [SF-36; physical (PCS) and mental (MCS) component score]) and total Sharp van der Heijde (SvdH) scores for each disease activity category were modelled using multi-level models. Covariates included year of onset, age, gender and DMARD use at first visit.

**Results.** Of 2701 patients, 562 (21%) were categorized mRDAS, 330 (12%) mLDAS, 279 (10%) sRDAS, 203 (7.5%) sLDAS and 93 (3%) sBR. Patients categorized as mRDAS had increasingly divergent improved HAQ, SF-36 PCS, MCS and total SvdH scores compared with mLDAS (*P*-values 0.001 to <0.0001, all time points). Patients categorized as sRDAS had better HAQ, SF-36 PCS and MCS scores (*P*-values 0.05 to <0.0001, all time points) and SvdH scores ($P = 0.05$, years 3–5) over sLDAS. sBR was associated with better HAQ, and SF-36 PCS and MCS scores over sLDAS (*P*-values 0.002 to <0.0001, all time points).

**Conclusion.** These findings from routine care support ACR/EULAR guidelines that remission is a preferable goal over low disease activity in early RA.

**Key words:** rheumatoid arthritis, remission, low disease activity, life quality, function, damage

**Rheumatology key messages**

- Function, quality of life and structural outcomes are significantly better in remission than low DAS in early RA.
- Differences are more striking using Boolean rather than DAS28 remission criteria.
- These findings support ACR/EULAR guidelines that in early RA the primary goal should be remission.

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## Introduction

Treat-to-target (T2T) principles are widely recognized as the best strategy to achieve optimal disease outcomes in RA [1]. Two target outcomes are proposed within both ACR and EULAR guidelines [2, 3] and these have been endorsed by national bodies such as the National Institute for Health and Care Excellence [4]. These targets are either remission or low disease activity, with any higher disease activity state regarded as inadequate disease control mandating a therapeutic change.

Whilst remission may be the optimal treatment target in RA, it is hard to achieve and sustain [5]; for example,





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sustained remission was reported in considerably less than 50% with early RA over 10 years (by various disease activity criteria) in the Swedish Rheumatology Quality registry [6]. In contrast, low disease activity, being a less stringent outcome criterion, is easier to achieve in routine practice, and tempting for the rheumatologist to adopt as a T2T goal. Furthermore, in routine practice adherence to treatment escalation when the target has not been achieved is low [7, 8], suggesting resistance either from the patient or health professional. Reasons for this might include satisfaction with the current overall health and functional status irrespective of DAS categorization, or concerns about dose-related treatment adverse effects.

Therefore, an important clinical question is whether there are important differences in outcomes between RA patients who achieve remission *vs* low disease activity. Comparison of HAQ and radiological damage progression in two early RA clinical trials in which the T2T strategy was steered to achieve either DAS remission (RDAS) or low DAS (LDAS) have shown no differences over 5 years [9]. However, this comparison was of the T2T intention rather than the actual disease activity achieved. As such, the actual DAS outcomes achieved in the RDAS and LDAS steered groups were overlapping at 5 years, with 61% achieving LDAS in both groups and 43 and 32% achieving RDAS in each group, respectively.

We have analysed real-life inception cohort early RA data from the Early Rheumatoid Arthritis Study (ERAS) and Network (ERAN), with up to 25-year follow-up, exploring differences in outcomes between patient groups who achieved different DAS categories. Previously we showed differences in HAQ and structural outcomes between moderate (3.2–5.1) and high (>5.1) DAS categories [10]. Here we report functional, Short Form 36 Health Survey Questionnaire (SF-36) and structural outcomes over 5 years in the ERAS and ERAN cohorts in patients achieving RDAS using DAS28 <2.6 and Boolean remission criteria compared with those achieving LDAS (DAS28 2.6–3.2).

## Methods

### Patient databases

The analysis was based on data from two large UK inception cohorts:

- The ERAS, a multi-centre inception cohort of 1465 patients with early RA [<2 years disease duration, no prior conventional synthetic DMARD (csDMARD)]. The recruitment period was 1986–99, across nine hospitals in England, followed yearly for up to 25 years (median follow up 10 years).
- The ERAN, a multi-centre inception cohort of 1236 early RA patients (<3 years disease duration). The recruitment period was 2002–12, across 23 centres in England, Wales and Ireland, followed yearly for up to 10 years (median follow up 6 years).

Recruitment was based on clinician diagnosis with 70% of patients fulfilling the minimum ARA criteria for RA [11] at baseline and 96% by last visit. Patients subsequently reclassified as non-RA were excluded from the study. Combined analysis of ERAS and ERAN was possible, being consecutive inception cohorts with a similar design and captured variables, as followed in previous analyses of these cohorts [10, 12–14]. Patients with at least 1 year of follow-up data were included. The ERAS study received ethical approval from the East Hertfordshire Local Research Ethics Committee and subsequently the Caldicott Guardian. The ERAN study received ethical approval from the Trent research ethics committee.

### Clinical, laboratory, functional and other variables

Information on clinical, laboratory, radiographic, functional features and treatment were recorded in both cohorts at baseline, between 3 and 6 months, at 12 months and then once yearly on standardized case report forms [13, 15, 16].

### Function and quality of life

HAQ as a measure of function was recorded at every patient visit. Data on health-related quality of life (QoL) were only available in ERAN, measured using the SF-36. Responses were grouped into physical component score (PCS) and mental component score (MCS). The PCS includes physical function, pain, physical role functioning and general health, whereas the MCS includes mental health, vitality, social functioning and social role functioning. Scores were normed to values from the general population in England [17] such that a score of 50 is indicative of the average level in the population. The minimal clinical important difference on an individual level was taken as 0.22 for HAQ, and 3.0 for SF-36 PCS and MCS.

### Disease activity

Disease activity was calculated according to the original three-variable method in ERAS (DAS) [18] and the more recent four-variable DAS28 [19] in ERAN. The original DAS was converted to DAS28 using a transformation formula developed by our team, to make the two comparable [20]. Disease activity was categorized by mean score over years 1–5 and by sustained scores at years 1 and 2 with remission defined as DAS28 <2.6 and low disease activity as DAS28 2.6–3.2. This resulted in the following patient groups: mean low disease activity years 1–5 (mLDAS), mean remission years 1–5 (mRDAS), sustained low disease activity years 1 and 2 (sLDAS), sustained remission years 1 and 2 (sRDAS) and sustained Boolean remission years 1 and 2 (sBR). Boolean remission was defined as: swollen joint count, tender joint count, patient global assessment, all $\leqslant 1$, and CRP $\leqslant 1$ mg/dl. Where a CRP was not available (60% of all observations), ESR was used at the level of $\leqslant 20$ mm/h, guided by the ACR/EULAR criteria for definition of remission [21, 22]. For categorization into sLDAS, sRDAS and sBR groups, DAS data had to be available at both year 1 and 2. For categorization into mLDAS and mRDAS groups a minimum of one DAS

data result from years 1–5 was accepted; however, two or more DAS scores were available for 86% of patients categorized as mRDAS and 92% of those categorized as mLDAS.

### Radiographic variables

Plain radiographs of hands and feet undertaken yearly were used to assess structural joint damage using the Sharp van der Heijde (SvdH) scoring method. This included radiographs from all 9 ERAS centres and 7/25 (28%) centres from ERAN, scored by two independent reviewers, as previously described [23]. The scores were combined to give a total SvdH score ranging from 0 to 448. The minimal clinical important difference on an individual level was taken as 5.0.

### Treatment

All centres managed RA according to local practice, influenced by contemporary UK guidelines for management of RA [24, 25] with treatment choice and strategy at the discretion of the treating clinician [26]. Median time to first csDMARD was 2 months after presentation in ERAS and 1 month after presentation in ERAN. Recruiting centres generally favoured SSZ as first csDMARD choice in ERAS with a gradual switch to MTX being observed, such that SSZ and MTX were used in equal proportions at the start of ERAN (2002) and then MTX became the most frequent first choice csDMARD thereafter [16]. At baseline all patients in ERAS were csDMARD naïve and in ERAN 13.5% had commenced a csDMARD within a few weeks of first secondary care visit. Combination csDMARDS were generally used for more severe RA and were introduced at earlier time points in the later years of ERAS and in 25% of those who received any csDMARDs in ERAN [16, 26]. In ERAN the most frequently used combinations of csDMARDs were MTX/SSZ, MTX/SSZ + HCQ and MTX/HCQ [26]. Only a small proportion of patients received biological DMARDs (bDMARDs), which were available from 2002 onwards (<2% by 1 year and <10% by 3 years).

### Statistical analysis

The primary analysis compared function, QoL and radiographic outcomes between the mRDAS and mLDAS groups. Secondary analyses compared the same outcomes between the sRDAS and sLDAS groups, and the sBR and sLDAS groups. Summary statistics were used to describe demographic and baseline data between the groups. HAQ, SF-36 PCS and SF-36 MCS progression between years 1 and 5 was estimated using linear mixed effects models, whilst progression of total SvdH scores between baseline and year 5 was estimated using negative binomial mixed effects models. Individual scores at each assessment between baseline and 5 years were included as outcome variables. All models incorporated a random intercept and a random slope for time. This accounts for the repeated observations within-individuals and allows the level of the outcome at baseline and the rate of change over time to vary across individuals. Missing data were inferred by full information maximum likelihood. Time was modelled using a linear spline with a change point at 12 months to account for the non-linear trajectory of all outcomes over time. This was due to outcomes typically showing an improvement in the first 12 months, when most initiated treatment, but then scores plateaued or worsened over the following 4 years. DAS28 category was included as dummy-coded variables with an interaction term with time. The first model looked at HAQ, SF-36 PCS, SF-36 MCS and SvdH outcomes in mRDAS *vs* mLDAS, whereas the second and third models looked at the same outcomes in sRDAS *vs* sLDAS and sBR *vs* sLDAS groups, respectively. To protect against confounding, the analysis controlled for age at RA onset, gender, calendar year of first visit, use of DMARD treatments at baseline and steroid prescription at baseline. All analyses were carried out in Stata V.15.1 (StataCorp LLC, College Station, TX, USA).

## Results

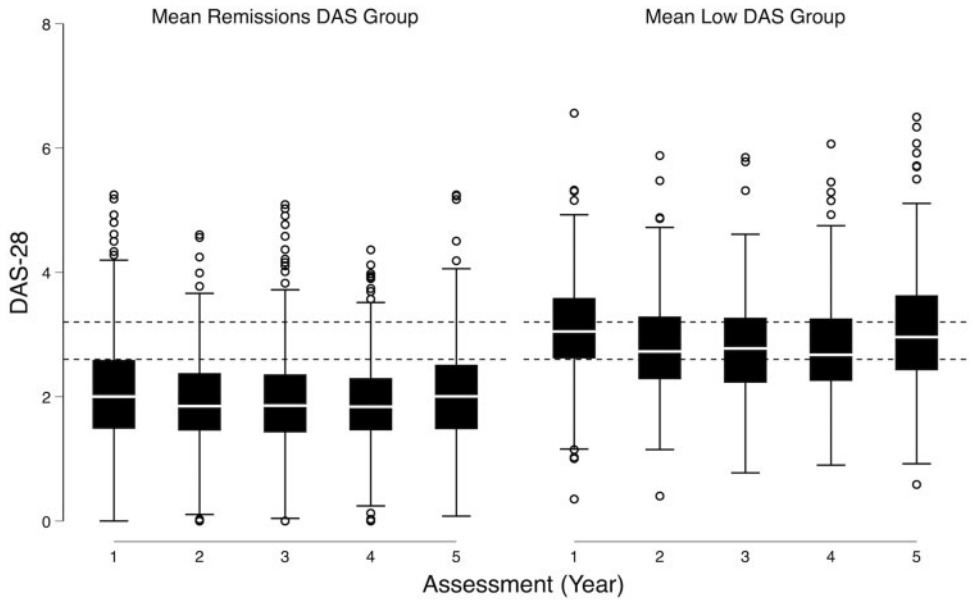
### Descriptive data

A total of 2701 patients were included in the analysis. Patients were allocated to the mRDAS and mLDAS groups on the basis of the mean DAS score over five annual assessments from years 1–5, meaning that scores were not necessarily consistently within the final allocated DAS group at every annual assessment. However, the median DAS28 scores of the mRDAS and mLDAS groups were within the allocated DAS28 categorical range at each annual time point, see Fig. 1. In the mRDAS group, at each year over 75% of patients had a DAS28 score in the RDAS range (supplementary Table S1, available at *Rheumatology* online) and 97% had more than half of their annual observations within their allocated RDAS range. In the mLDAS group there was more variability, with 23–37% of patients having a DAS28 score in the LDAS range at each year (supplementary Table S2, available at *Rheumatology* online), and 34% having more than half of their five annual observations within the LDAS range. Reasons for early discontinuation and missing data are shown in supplementary Table S3, available at *Rheumatology* online.

Four patients fulfilled criteria for both sBR and sLDAS, as the highest permissible scores to satisfy Boolean remission (allowing ESR up to 20 mm/h) produces a DAS28 ESR 3.1 and DAS28 CRP 2.8, both of which are in the LDAS category. As Boolean remission is the most stringent outcome criterion, it was considered clinically and statistically appropriate to include these four patients in the less strict sLDAS group for comparison purposes between sLDAS and sBR. Sensitivity analysis excluding these four overlapping patients made no difference to the overall results.

Table 1 shows the numbers categorized as mRDAS, mLDAS, sRDAS, sLDAS and sBR, and their baseline demographic and RA specific covariates. Several baseline covariates were statistically different between the mRDAS

**Fig. 1** Box plot of DAS28 scores over years 1–5 for the mean remission DAS group, and the mean low DAS group




The white line in the middle of the boxes represents the median values, whilst the outer part of the boxes indicates the 25th and 75th percentiles. The whiskers extending from the boxes indicate the upper and lower adjacent values (within 1.5× IQR of the median), whilst the circles outside the whiskers represent outside values. The black dashed lines across the plots indicate the threshold for remission DAS (2.6) and low DAS (3.2) categorization. IQR: interquartile range.

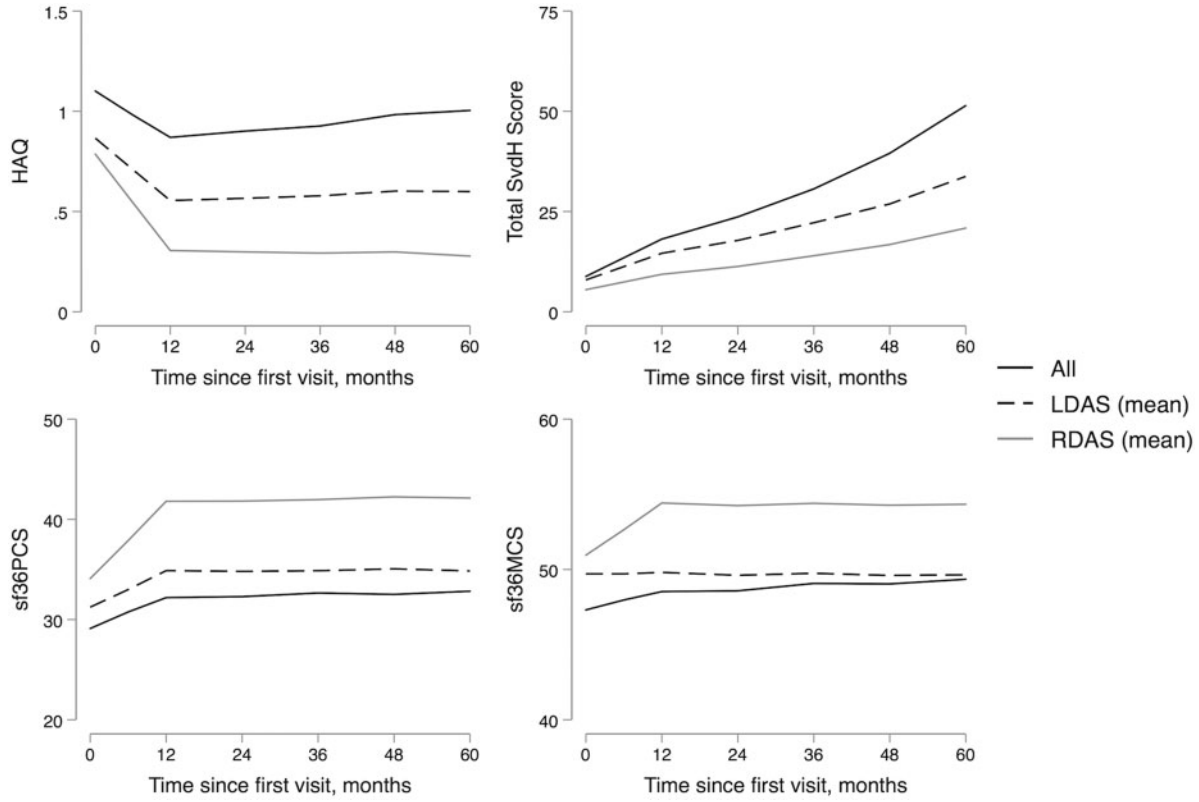
**Table 1** Patient demographic and baseline covariates by DAS28 category

| | mRDAS | mLDAS | *P** | sRDAS | sLDAS | *P*** | sBR |
|---|---|---|---|---|---|---|---|
| *N* (%) | 562 (21) | 330 (12) | | 279 (10) | 203 (7.5) | | 89 (3) |
| Age, years [mean (S.D.)] | 53.8 (14.35) | 56.1 (13.12) | 0.014 | 53.5 (14.23) | 55.5 (14.29) | 0.135 | 51.6 (15.87) |
| Female [*n* (%)] | 288 (51.3) | 205 (62.1) | 0.002 | 140 (50.2) | 120 (59.11) | 0.052 | 45 (50.6) |
| RF positive [*n* (%)][a] | 303 (57.4) [528] | 186 (60.2) [309] | 0.426 | 161 (60.5) [266] | 115 (59.6) [193] | 0.839 | 55 (63.2) |
| BMI [mean (S.D.)][a] | 26.0 (4.09) [497] | 26.3 (4.49) [304] | 0.262 | 25.6 (4.02) [255] | 26.0 (4.38) [178] | 0.321 | 25.7 (4.08) |
| Current smoker [*n* (%)] | 94 (20.6) | 67 (26.2) | 0.226 | 39 (17.9) | 36 (23.2) | 0.348 | 9 (13.0) |
| Ex-smoker [*n* (%)] | 132 (28.9) | 70 (27.3) | | 69 (31.7) | 41 (26.5) | | 23 (33.3) |
| Never smoker [*n* (%)] | 231 (50.6) | 119 (46.5) | | 110 (50.5) | 78 (50.3) | | 37 (53.6) |
| Missing data [*n* (%)] | 105 (18.7) | 74 (22.4) | | 61 (21.9) | 48 (23.6) | | 20 (21.5) |
| ESR mmHg/h [median (IQR)][a] | 20 (27) [510] | 29 (35) [307] | <0.001 | 20 (32) [261] | 27.5 (38) [190] | 0.015 | 28.5 (34.5) [84] |
| Hb g/dl [mean (S.D.)][a] | 13.2 (1.44) [552] | 13.1 (1.41) [326] | 0.334 | 13.2 (1.41) [275] | 13 (1.42) [201] | 0.241 | 13 (1.45) [87] |
| DAS28 [mean (S.D.)][a] | 4.1 (1.51) [542] | 4.4 (1.34) [316] | 0.001 | 4.1 (1.54) [273] | 4.4 (1.32) [198] | 0.009 | 4.1 (1.53) [87] |
| SvdH [median (IQR)][a] | 6 (14) [302] | 7 (19) [195] | 0.045 | 6 (15) [169] | 7 (16) [120] | 0.171 | 6 (13) [55] |
| HAQ [mean (S.D.)][a] | 0.8 (0.70) [552] | 0.9 (0.68) [324] | 0.023 | 0.8 (0.71) [276] | 0.9 (0.74) [200] | 0.132 | 0.7 (0.73) [88] |
| SF-36 MCS [mean (S.D.)][a] | 51.2 (10.68) [242] | 50.2 (11.81) [112] | 0.394 | 52.6 (10.07) [90] | 51.7 (10.64) [52] | 0.631 | 56.3 (9.08) [31] |
| SF-36 PCS [mean (S.D.)][a] | 34.8 (12.14) [242] | 30.1 (11.89) [112] | 0.001 | 36.2 (12.56) [90] | 33.5 (11.86) [52] | 0.22 | 41.6 (11.97) [31] |

All variables shown as mean values, except medians for ESR and SvdH. SF-36 scores were only available from ERAN. T-test for continuous variables, Chi-squared for categorical variables, Mann–Whitney U (non-parametric) for ESR and SvdH. [a]Number with available data given in square brackets. *mRDAS *vs* mLDAS. **sRDAS *vs* sLDAS. mRDAS: mean remission DAS; mLDAS: mean low DAS; sLDAS: sustained low DAS; sRDAS: sustained remission DAS; sBR: sustained Boolean remission; IQR: interquartile range; SvdH: Sharp van der Heijde; SF-36: Short Form 36 Health Survey Questionnaire; MCS: mental component score; PCS: physical component score.

and mLDAS groups, including age, gender, ESR, DAS28, HAQ, SvdH score and SF-36 PCS, with more severe or worse scores in the patients categorized mLDAS. The statistically different baseline covariates between the sRDAS and sLDAS groups were higher proportion female, ESR and DAS28 in the sLDAS group.

FIG. 2 HAQ, SF-36 MCS, SF-36 PCS and total SvdH estimated mean scores in entire ERAS/ERAN cohort and patients categorized as mLDAS and mRDAS




Patients categorized as mean LDAS or mean RDAS based on mean score from years 1, 2 3, 4 and 5. Analysis controlled for year of recruitment, age of RA onset, gender and baseline treatment. SF-36: Short Form 36 Health Survey Questionnaire; MCS: mental component score; PCS: physical component score; SvdH: Sharp van der Heijde; ERAS/ERAN: Early Rheumatoid Arthritis Study/Early Rheumatoid Arthritis Network; mLDAS: mean low DAS; mRDAS: mean remission DAS.

### Outcomes in mRDAS *vs* mLDAS groups, adjusted model

The estimated mean scores in the adjusted mixed effects models from baseline to year 5 for each of the functional, QoL and radiographic outcomes (HAQ, SF-36 MCS, SF-36 PCS and total SvdH scores), in patients categorized as mRDAS, mLDAS and the entire ERAS/ERAN cohort, are shown in Fig. 2. For all outcomes the differences in mean scores between the mRDAS and mLDAS groups at each year 1–5 time point were highly statistically different (*P*-value 0.001 to <0.0001), and increasingly divergent with each successive year in favour of mRDAS, see Table 2. In relation to the minimally clinical important difference for an individual, for each outcome the group differences exceeded this threshold. When controlling for additional baseline covariates (ESR, BMI, pain, comorbidities, social deprivation, DAS28 and smoking), the effects comparing mLDAS *vs* mRDAS remain significant (data not shown). Repeating the analyses restricted to patients with three or more DAS values available from years 1–5 for allocation to either mRDAS or mLDAS groups resulted in no difference in the pattern or statistical significance of the outcomes.

### Outcomes in sRDAS *vs* sLDAS groups and sBR *vs* sLDAS adjusted models

The estimated mean scores in the adjusted mixed effects models from baseline to year 5 for each of the functional, QoL and radiographic outcomes (HAQ, SF-36 MCS, SF-36 PCS and total SvdH scores), in patients categorized as sRDAS, sLDAS and the entire ERAS/ERAN cohort, are shown in Fig. 3, and in patients categorized as sBR, sLDAS and the entire ERAS/ERAN cohort in supplementary Fig. S1, available at *Rheumatology* online.

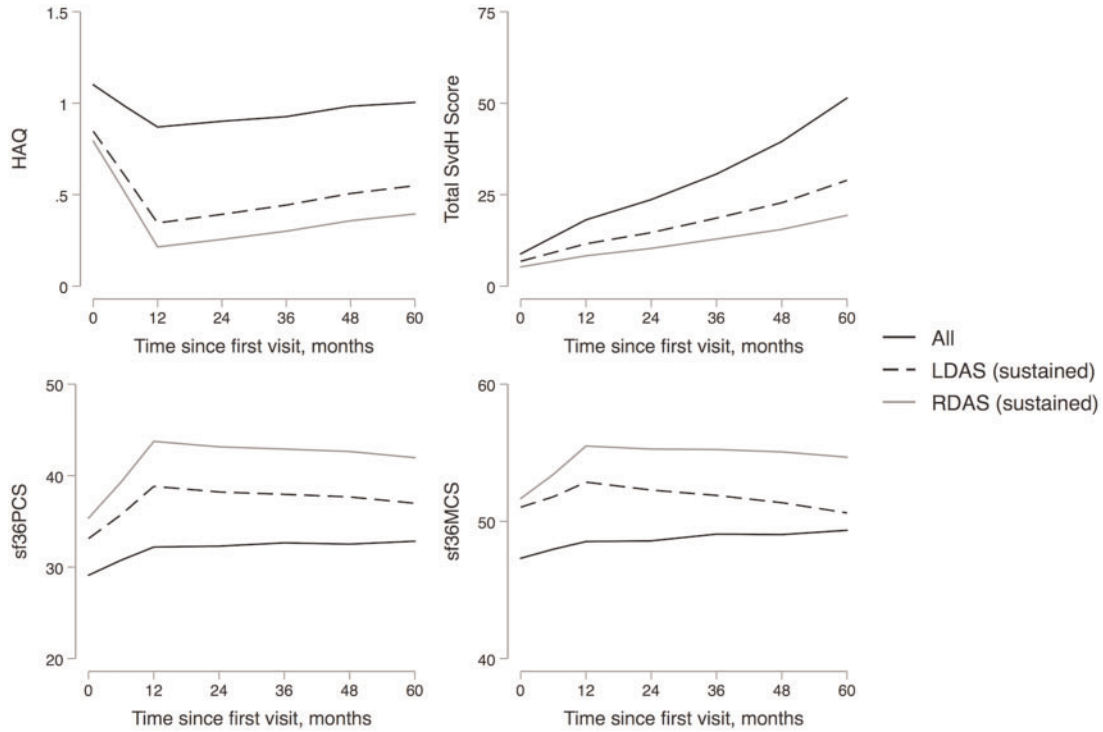
Comparing the sRDAS *vs* sLDAS groups (Table 3), mean HAQ, SF-36 MCS, SF-36 PCS and total SvdH scores were increasingly divergent with each successive year, favouring sRDAS over sLDAS, and were statistically significant from year 1 onwards for HAQ, SF-36 MCS and PCS (*P*-value 0.05 to <0.0001) and from year 3 for SvdH ($P = 0.05$). In relation to the minimal clinically important difference (MCID) for an individual, the mean differences

**Table 2** Difference in estimated mean scores (95% CI) per year between mLDAS and mRDAS groups

| | MCID | Baseline | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|---|---|
| HAQ | 0.22 | 0.10 (0.03–0.18) $P = 0.007$ | 0.27 (0.20 – 0.34) $P < 0.0001$ | 0.29 (0.23 – 0.35) $P < 0.0001$ | 0.31 (0.24 – 0.37) $P < 0.0001$ | 0.33 (0.26 – 0.40) $P < 0.0001$ | 0.34 (0.27 – 0.42) $P < 0.0001$ |
| SF-36 MCS | 3.0 | 1.41 (−0.68 to 3.51) NS | 4.78 (6.85 – 2.71) $P < 0.0001$ | 4.80 (6.62 – 2.98) $P < 0.0001$ | 4.82 (6.65 – 2.99) $P < 0.0001$ | 4.84 (6.93 – 2.75) $P < 0.0001$ | 4.86 (7.39 – 2.34) $P < 0.0001$ |
| SF-36 PCS | 3.0 | 3.46 (5.76 – 1.16) $P = 0.003$ | 7.51 (9.78 – 5.24) $P < 0.0001$ | 7.61 (9.61 – 5.61) $P < 0.0001$ | 7.70 (9.71 – 5.70) $P < 0.0001$ | 7.80 (10.09 – 5.51) $P < 0.0001$ | 7.90 (10.66 – 5.13) $P < 0.0001$ |
| Total SvdH | 5.0 | 2.41 (0.65 – 4.17) $P = 0.007$ | 5.20 (2.07 – 8.32) $P = 0.001$ | 6.44 (2.76 – 10.13) $P = 0.001$ | 8.15 (3.61 – 12.70) $P < 0.0001$ | 10.05 (4.46 – 15.64) $P < 0.0001$ | 12.77 (5.49 – 20.04) $P = 0.001$ |

mLDAS: mean low DAS; mRDAS: mean remission DAS; MCID: minimal clinically important difference; SF-36: Short Form 36 Health Survey Questionnaire; MCS: mental component score; PCS: physical component score; SvdH: Sharp van der Heijde.

**Fig. 3** HAQ, SF-36 MCS, SF-36 PCS and total SvdH estimated mean scores in entire ERAS/ERAN cohort and patients categorized as sLDAS and sRDAS




Patients categorized as sustained LDAS or sustained RDAS based on outcomes at both year 1 and 2. Analysis controlled for year of recruitment, age of RA onset, gender and baseline treatment. SF-36: Short Form 36 Health Survey Questionnaire; MCS: mental component score; PCS: physical component score; SvdH: Sharp van der Heijde; ERAS/ERAN: Early Rheumatoid Arthritis Study/Early Rheumatoid Arthritis Network; sLDAS: sustained low DAS; sRDAS: sustained remission DAS.

between the groups were in excess of the threshold for SF-36 PCS scores from year 1, for SF-36 MCS from year 2 and for SvdH from year 3, but not greater than this threshold for HAQ.

Comparing outcomes in the sBR *vs* sLDAS groups (supplementary Table S4, available at *Rheumatology* online), mean HAQ, SF-36 PCS and SF-36 MCS scores were all highly statistically significantly better in the sBR group

**Table 3** Difference in estimated mean scores (95% CI) per year in sLDAS *vs* sRDAS groups

| | MCID | Baseline | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|---|---|
| HAQ | 0.22 | 0.07<br>(0.17 – 0.02)<br>NS | 0.15<br>(0.24 – 0.06)<br>$P = 0.001$ | 0.16<br>(0.24 – 0.08)<br>$P < 0.0001$ | 0.17<br>(0.24 – 0.08)<br>$P < 0.0001$ | 0.17<br>(0.26 – 0.08)<br>$P < 0.0001$ | 0.18<br>(0.27 – 0.08)<br>$P < 0.0001$ |
| SF-36 MCS | 3.0 | 0.81<br>(2.20 – 3.83)<br>NS | 2.82<br>(0.00 – 5.64)<br>$P = 0.05$ | 3.18<br>(0.66 – 5.70)<br>$P = 0.01$ | 3.54<br>(0.99 – 6.09)<br>$P = 0.006$ | 3.90<br>(1.02 – 6.79)<br>$P = 0.008$ | 4.26<br>(0.81 – 7.72)<br>$P = 0.015$ |
| SF-36 PCS | 3.0 | 2.80<br>(0.60 – 6.21)<br>NS | 5.50<br>(2.32 – 8.67)<br>$P = 0.01$ | 5.53<br>(2.71 – 8.35)<br>$P < 0.0001$ | 5.56<br>(2.70 – 8.41)<br>$P < 0.0001$ | 5.59<br>(2.33 – 8.85)<br>$P = 0.001$ | 5.62<br>(1.69 – 9.54)<br>$P = 0.005$ |
| Total SvdH | 5.0 | 1.47<br>(−3.72 to 0.79)<br>NS | 3.14<br>(−6.83 to 0.55)<br>NS | 4.14<br>(−8.65 to 0.38)<br>NS | 5.49<br>(−11.17 to 0.19)<br>$P = 0.058$ | 7.02<br>(−14.06 to 0.02)<br>$P = 0.051$ | 9.23<br>(−18.33 to −0.12)<br>$P = 0.047$ |

sLDAS: sustained low DAS; sRDAS: sustained remission DAS; SvdH: Sharp van der Heijde; SF-36: Short Form 36 Health Survey Questionnaire; MCS: mental component score; PCS: physical component score; MCID: minimal clinically important difference; NS: not significant.

from year 1 onwards (*P*-value 0.002 - <0.0001), and increasingly divergent for HAQ and SF-36 MCS with each successive year. Total SvdH mean scores showed increasingly divergent less radiographic progression in sBR *vs* sLDAS at all time points, but this did not reach statistical significance. In relation to the MCID for an individual, the group differences exceeded this threshold for HAQ, SF-36 MCS and SF-36 PCS at all time points, and for total SvdH score at year 4 and 5. The differences in HAQ, SF-36 MCS and SF-36 PCS mean scores between the sBR and sLDAS groups were much greater than the comparison between sRDAS and sLDAS (see Table 3 and supplementary Table S4, available at *Rheumatology* online). At year 5 the difference in mean scores, respectively, were HAQ 0.35 and 0.18, SF-36 MCS 9.27 and 4.26, and SF-36 PCS 8.48 and 5.62. Using the alternate Boolean definition criterion of ESR <10 mmHg/h (rather than 20 mmHg/h) for those cases where CRP was not available, or ESR <20 mmHg/h for all cases, resulted in no difference to the pattern or significance of results across all outcomes.

## Discussion

This study reports significant and increasingly divergent differences in functional, QoL and radiographic outcomes over 5 years, favouring patients in remission over low disease activity in the ERAS and ERAN inception cohorts. These findings reflect outcomes from a conservative treatment approach, in routine care, at a time when more aggressive T2T strategies and bDMARDs were yet to be widely introduced. Nonetheless, for those patients who achieved remission (DAS28 <2.6), whether defined by mean scores from year 1–5 or by sustained scores at years 1 and 2, outcomes were significantly better than those achieving low disease activity (DAS28 2.6–3.2). The magnitude of difference on a group level was in excess of the MCID threshold used to assess individual outcomes for each of HAQ, SF-36 MCS, PCS and SvdH scores at every time point over 5 years comparing mRDAS with mLDAS, and at many time points comparing sLDAS with either sRDAS or sBR.

The DAS28 definition of remission is the least stringent composite measure, in comparison with Boolean criteria or the Simplified/Clinical Disease Activity Indices (SDAI, CDAI). As such our finding of significant differences across all outcomes between low disease activity and the DAS28 definition of remission emphasizes the clinical importance of these data. A more stringent criteria of remission would predict even greater differences in outcomes compared with low disease activity. Using the Boolean criteria of remission, we found greater differences in HAQ and SF-36 MCS and PCS outcomes in the sLDAS *vs* sBR models than in the sLDAS *vs* sRDAS models. This was not the case for the total SvdH score. This may reflect greater statistical uncertainty as there were fewer individuals in the sBR than sRDAS categories. However, it is noteworthy that whilst Boolean criteria are strict on all components, with scores for patient global assessment, swollen joint count, tender joint count and CRP (mg/dl) all required to be <1, the equivalent quoted ESR is up to 20 mm/h in men and 30 mm/h in women [21, 22]. The ESR is influenced by age, haemoglobin, RF and total immunoglobulins, thus making it a less standardized measure of the inflammatory response. We allowed an ESR up to 20 mm/h for men and women to fulfil Boolean remission for individuals where CRP was not available (60% of all observations). We suspect this may be too high and potentially a reason for greater radiographic progression in those allocated to the sBR group, and hence an absence of significant difference in total SvdH scores between the sBR and sLDAS groups. In keeping with this, O'Dell and Mikuls found in the Veterans Affairs RA registry that a lower ESR <10 mm/h was a reasonable surrogate for a CRP <1 mg/dl [27]. Our data may therefore be a conservative estimate of sBR associations with outcomes; however, repeating the analysis with ESR <10 mm/h as the criterion for inclusion in sBR continued to show non significance in mean total SvdH scores between sBR and sLDAS groups at all time points.

Our findings apply to early RA and are not necessarily generalizable to patients with disease duration beyond 5 years. Indeed, EULAR guidelines state that an LDAS target applies especially to patients who have failed previous therapies [2], and who are therefore likely to have longer standing disease. This reflects the fact that some items of the composite outcome scores that are used, such as the patient global score and tender joint counts in CDAI and DAS28, may lose plasticity in chronic disease, given accrued joint damage, non-inflammatory pain and changes in mental health. In such cases improving the DAS into the remission range may be difficult to achieve, or inappropriate to attempt by escalation of immune suppression. We therefore emphasize that our findings only support EULAR and ACR guidelines to aim for remission in patients with early disease.

Our data are in keeping with findings from the Canadian Early Arthritis Cohort (CATCH) at year 2, where HAQ and visual analogue scale scores for pain and fatigue were significantly better for those achieving sustained remission compared with sustained low disease activity (both defined by CDAI or SDAI), with the magnitude also in excess of MCID for HAQ on a group level [28].

Striving to achieve remission over low disease activity has implications for clinical practice. In ERAS/ERAN there was no protocolized treatment approach, with contemporary conservative use of csDMARDs in most patients, and a relatively low proportion achieving DAS28 remission as a consequence. Adopting a rigorous T2T strategy is likely to lead to more patients achieving remission, notwithstanding the resource implications of more clinical appointments, increased health-related administrative costs, use of higher doses of therapies with associated monitoring and toxicity costs, and more patients progressing to high-cost targeted synthetic DMARDs or bDMARD. Nonetheless, data indicate that when used as intended, intensely and in combination, csDMARDs can be very effective in early RA [29], and T2T strategies cost effective in early RA [30]. However, it is worth remembering that real-world data indicate poor adherence of patients and physicians to T2T strategies [7, 8].

The strength of this study is inherent in the nature of ERAS and ERAN, two real-world large inception early RA cohorts, recruiting all-comers, treated according to contemporary best practice, with the rigour of regular standardized assessments and data collection, allowing data to be pooled and analysed collectively. In contrast to randomized controlled trials, the data from ERAS and ERAN are not restricted to defined RA populations with strict inclusion and exclusion criteria, nor to treatment strategies confined by protocol. ERAS and ERAN are also unique in size, recruiting 2701 patients.

A limitation of this study is that patients did not achieve consistently, over 5 years, the DAS outcome of the group to which they were allocated. Although patients allocated to the mRDAS group showed very high adherence to remission DAS scores from year 1–5, the lower adherence in patients allocated to mLDAS was inevitable given the much narrower range of scores fulfilling this criterion (2.6–3.2). Where scores in patients allocated to mLDAS deviated, they did so as much into the RDAS as into higher DAS categories (supplementary Table S2, available at *Rheumatology* online). This reflects real-world variations in disease activity that are characteristic of RA. That such significant and clinically meaningful differences were seen in this situation we believe makes these findings all the more powerful, given the increasing divergence in functional, QoL and structural outcomes favouring mRDAS over mLDAS from years 1–5. Other limitations are the historical nature of the ERAS and ERAN cohorts at a time when T2T strategies, first-line combination csDMARDs and early escalation to bDMARDs were not widely used, and this is likely the reason why the overall proportion of patients achieving remission and low disease activity was low.

In conclusion, we have shown highly significant and clinically meaningful associations between improved functional, QoL and structural outcomes in early RA patients achieving remission compared with low disease activity up to year 5 in the ERAS/ERAN real-world inception cohorts. These findings come from analyses using the least strict criterion of remission in clinical practice, based on the DAS28 score, either defined by mean values from year 1–5 or on sustained values at year 1 and 2. Analyses using the stricter Boolean remission criterion reveals more striking differences in function and QoL outcome measures compared with patients achieving low disease activity. These findings support ACR and EULAR guidelines that in early RA the primary goal should be remission.

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## Supplementary data

Supplementary data are available at *Rheumatology* online.

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