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# Chapter 10

Is achieving remission associated with better health related quality of life than maintaining low disease activity in rheumatoid arthritis patients?

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**1 ABSTRACT**

2  
3 **Objective** To assess if achieving remission is associated with a better health related  
4 quality of life (HRQoL) than maintaining low disease activity (LDA).

5 **Methods** Data were used of 508 patients with recent onset rheumatoid arthritis (RA)  
6 participating in the BeSt study, whose treatment was steered at LDA ( $DAS \leq 2.4$ ), to  
7 investigate the relationship between DAS and HRQoL. Two summary scales of the Short  
8 Form-36 were used: the Physical and Mental Component Scale (PCS, MCS). Three linear  
9 mixed models were specified with PCS/MCS as dependent variable and with disease  
10 activity category, change in DAS score or change in disease activity category as inde-  
11 pendent variables. Remission was defined as  $DAS < 1.6$ , or, separately, according to the  
12 ACR/EULAR remission criteria.

13 **Results** Patients in remission ( $DAS < 1.6$ ) compared to LDA had a significantly better PCS  
14 and MCS, with a difference of 4.0 and 1.0 points respectively ( $p < 0.001$ ). An increase of 1  
15 point in DAS was associated with a decrease of 4.6 (95% CI 4.4;4.8) in PCS and a decrease  
16 of 1.6 (95% CI 1.3;1.9) in MCS. Achieving DAS-remission resulted in a 3.8 point gain in  
17 PCS compared to maintaining LDA, but no difference in MCS. Similar results were found  
18 for remission according to the ACR/EULAR criteria.

19 **Conclusion** Improvement of disease activity is associated with improvement of HRQoL,  
20 with also a clinically relevant improvement in PCS score for patients achieving remission  
21 when compared to maintaining LDA. Patients who move from LDA to remission gain 4  
22 points in PCS, but show no significant improvement in MCS.

## 1 INTRODUCTION

2  
3 Advances in treatment for RA patients have led to improved clinical and structural  
4 outcomes. Following recent recommendations, treatment should be started early and  
5 requires adjusting the medication until a target of remission or at least low disease  
6 activity (LDA) is achieved.<sup>1,2</sup> Achieving such a target is associated with better functional  
7 ability and less radiological damage.<sup>3</sup>

8 It remains unclear if it would be better to treat to the target of remission than of LDA  
9 as comparative studies are lacking. Also, the influence on Health Related Quality of Life  
10 (HRQoL), of achieving these different levels of disease activity is uncertain. As HRQoL re-  
11 flects a more broad perspective of the influence of disease on daily life than most outcome  
12 measures, it may give more guidance on which disease activity level should be preferred.  
13 Therefore we investigated in a low disease activity targeted cohort including early  
14 RA patients whether 1) remission or achieving remission was associated with a better  
15 HRQoL than LDA or maintaining LDA and whether 2) a change in disease activity was  
16 associated with a relevant change in HRQoL.

## 17 18 19 METHODS

### 20 21 *Patients*

22 Five-year follow-up data from the BeSt trial were used, where 508 patients with recent  
23 onset active RA were dynamically treated according to a step-wise treatment protocol  
24 aiming at a disease activity score (DAS)  $\leq 2.4$ . Patients were randomized to four different  
25 treatment strategies: 1. sequential monotherapy; 2. step-up combination therapy; 3.  
26 initial combination therapy with prednisolone and 4. initial combination therapy with  
27 infliximab. Clinical assessment of disease activity was performed every three months,  
28 and included a joint count for tenderness and swelling, erythrocyte sedimentation rate  
29 (ESR) and patient's assessment of global disease activity. This study was approved by the  
30 ethical committees of participating centers and all patients provided informed consent.  
31 More details about the BeSt study have been described elsewhere.<sup>4</sup>

### 32 33 *Outcome assessment*

34 HRQoL was assessed with the Short Form 36 version 2 (SF-36),<sup>5</sup> which covers eight do-  
35 mains of health status: physical functioning, role-physical, bodily pain, general health,  
36 vitality, social functioning, role-emotional, and mental health. The SF-36 score ranges  
37 from 0 (worst) to 100 (best) and norm based scoring is available to compare different  
38 populations. Two summary measures, representing the physical component of HRQoL  
39 (physical component scale; PCS) and the mental component of HRQoL (mental compo-

1    nent scale; MCS) are available. Both scales cover all HRQoL domains but more weight is  
2    given to physical functioning, role-physical, bodily pain and general health in the PCS,  
3    whereas more weight is given to vitality, social functioning, role-emotional and mental  
4    health in the MCS. The SF-36 was filled out every 3 months in the first two years of treat-  
5    ment and yearly thereafter. A clinically important improvement from baseline for RA  
6    patients has previously been established as a minimum of 2.5 to 5 points improvement  
7    for the two summery measures.<sup>6</sup>

### 9    *Statistical methods*

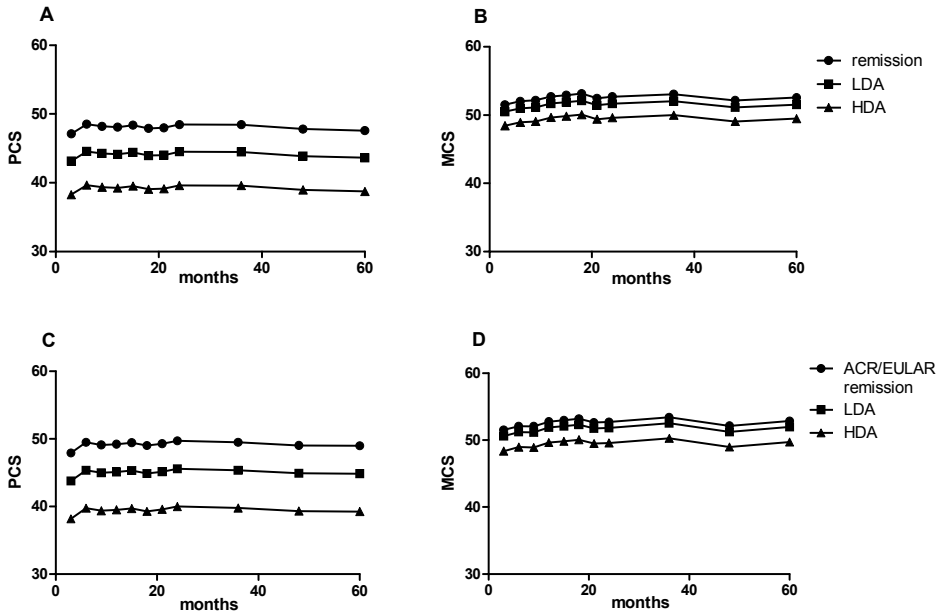
10   Statistical analyses were performed with the software program SPSS version 20.0 (SPSS,  
11   Chicago, Illinois). Linear mixed models (LMM) were used to investigate the association  
12   between disease activity (levels) and HRQoL over time, while correcting for within patient  
13   correlation. For all analyses the unstructured covariance matrix was used, which does not  
14   assume a specific covariance structure and estimates every variance and correlation.

15   Two continuous outcomes, both of which normally distributed, were used for all  
16   analyses: the PCS and the MCS. Three models with these outcomes and the following  
17   independent variables were used: 1) disease activity category, 2) delta DAS (absolute),  
18   previous DAS and previous PCS or MCS score and 3) change in disease activity category  
19   (remission to LDA and vice versa) and previous PCS or MCS score.

20   For the first and third model, patients were categorized according to their disease activ-  
21   ity category: high disease activity, low disease activity (based on the DAS), or remission.<sup>7</sup>

22   Remission was defined as  $DAS < 1.6$ ,<sup>8</sup> or, in a separate analysis, according to the ACR/  
23   EULAR remission criteria.<sup>9</sup> Patients were first divided into ACR/EULAR remission yes/no,  
24   and patients not in ACR/EULAR remission were then classified into low or high disease  
25   activity depending on their DAS. The ACR/EULAR remission criteria were not designed to  
26   compare against DAS categories, but as there is no alternative classification method that  
27   allows for comparison of ACR/EULAR remission against other levels of disease activity  
28   we used this approach. In model 3, all possible changes were included in the model.

29   We first used staying in low disease activity as reference category and then staying in  
30   remission and will only report on changing from low disease activity to remission and  
31   vice versa. Time was added as categorical covariate in all models in order to estimate the  
32   effect for each time point separately. The baseline visit was excluded because none of  
33   the patients were in remission at this visit. The following potential baseline confounders  
34   were considered: age, gender, HAQ, DAS, erosions (yes/no), anti-citrullinated protein  
35   antibodies, duration of complaints at inclusion, smoking, body mass index (BMI), alcohol  
36   intake and treatment group. None of the potential confounders importantly altered  
37    $\beta$ -estimates or p-values when added to the model as separate variable, so these were  
38   not included in the final models. Values for mean HRQoL at each time point per disease  
39   activity category were calculated using Estimated Marginal Means. (*figure 1*)



**Figure 1:** Health Related Quality of Life (HRQoL) per disease activity level over time depicted as mean Physical Component Scale score (PCS, panel a and c) and mean Mental Component Scale score (MCS, panel b and d) over time

## RESULTS

In total 508 patients with a mean (SD) DAS at baseline of 4.4 (0.9) were included. Mean PCS (SD) was 38.8 (7.9) and mean MCS at baseline was (47.0 (11.4)). At year 5, DAS was reduced to a mean (SD) level of 1.7 (0.8) while PCS and MCS had improved to a mean (SD) level of 44.8 (9.8) and 52.4 (8.6) respectively. Over 5 years (excluding the baseline evaluation), DAS-remission was recorded in 34% of the evaluations, while ACR/EULAR remission was recorded in 15%.(table 1)

**Table 1:** percentage of patients per disease activity category using two remission definitions for year 0-5 excluding the baseline visit

	Remission: DAS<1.6 (n visits =4941)	ACR/EULAR Remission criteria (n visits=4499)*
Remission	1667 (34%)	662 (15%)
Low disease activity	1704 (35%)	2384 (53%)
High disease activity	1570 (32%)	1453 (32%)

DAS disease activity score, n number, ACR American College of Rheumatology, EULAR European League Against Rheumatism

\*For 442 visits, patients could not be classified because of missing values for C-reactive protein

Low disease activity: DAS  $\leq$ 2.4, but not remission, High disease activity: DAS >2.4

### 1 Absolute disease activity scores in relation to QoL scores

2 Remission (DAS<1.6) was associated with a clinically relevant higher PCS than higher  
 3 levels of disease activity, with a dose response relationship. The difference in PCS when in  
 4 remission with PCS when in LDA ( $\beta$ ) was 4.0, and the difference with HDA 8.8, all  $p<0.001$ .  
 5 (table 2, figure 1) Likewise, DAS categories with lower DAS were associated with higher  
 6 MCS, although differences were smaller: LDA  $\beta=1.0$ , HDA  $\beta=3.1$ . Repeating the analyses  
 7 with remission according to the ACR/EULAR remission criteria gave similar results. (table  
 8 2) The univariable analysis showed that DAS category, gender, time, treatment group,  
 9 alcohol intake, BMI and baseline DAS were also associated with outcome PCS, and DAS  
 10 category, time, gender, baseline erosiveness (yes/no), baseline smoking status and base-  
 11 line DAS were univariable predictors for MCS. Of the possible confounding variables  
 12 none had a significant effect on the  $\beta$ -estimates per disease activity category when  
 13 added separately to the model, neither on the outcome PCS nor on MCS.

14 Changes in disease activity scores in relation to changes in HRQoL scores Absolute  
 15 changes in DAS scores were significantly associated with changes in both PCS and MCS.  
 16 Patients showed an increase of 4.6 (95% CI 4.4;4.8) points in PCS when decreasing 1  
 17 point in DAS, independent of their previous DAS score and previous PCS ( $p<0.001$ ). Simi-  
 18 lar results are seen for the MCS, however this difference is smaller: 1.6 (95% CI 1.3;1.9)  
 19 points ( $p<0.001$ ) improvement in MCS per 1 point decrease in DAS. The interaction term  
 20 between previous DAS and DAS change was not significant, implying that the relation-  
 21 ship between change in DAS and change in PCS/MCS is independent of the preceding  
 22 DAS level.

### 23 Changes in DAS category in relation to change in PCS and MCS

24 For patients who had LDA, achieving remission was associated with a significant im-  
 25 provement in PCS of 3.8 points, when compared to patients who stayed in LDA, but  
 26

27  
 28 **Table 2:** difference in absolute physical component scale score and mental component scale score  
 29 for patients in low and high disease activity compared to patients in remission, defined as DAS<1.6 or  
 30 according to the ACR/EULAR remission criteria

	PCS		MCS	
	<i>ref</i> (defined as DAS<1.6)	<i>ref</i> (defined according to ACR/ EULAR criteria)	<i>ref</i> (defined as DAS<1.6)	<i>ref</i> (defined according to ACR/EULAR criteria)
LDA	4.0 (3.5;4.4)	4.1 (3.5;4.8)	1.0 (0.5;1.5)	0.9 (0.2;1.6)
HAD	8.8 (8.3;9.4)	9.7 (9.0;10.5)	3.1 (2.5;3.7)	3.1 (2.3;3.9)

36 PCS physical component scale score Short form 36 (SF36), MCS mental component scale score SF36, DAS  
 37 disease activity score, LDA low disease activity (DAS  $\leq$ 2.4, but not remission), HDA high disease activity  
 38 (DAS>2.4), *ref* reference

39 Data are presented as  $\beta$  estimates (95% CI), representing the estimated difference with the reference  
 category in PCS or MCS score



no improvement in MCS.(table 3) Patients who had been in remission but flared to LDA showed a 4.0 point deterioration in PCS when compared to patients who stayed in remission, and no change in MCS.

**Table 3:** change in component score (physical component scale score and mental component scale score) when achieving remission from low disease activity, and loosing remission to low disease activity, with remission defined as \*DAS<1.6 and \*\*according to the ACR/EULAR remission criteria

	PCS		MCS	
Staying in low disease activity	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>
Achieving remission from low disease activity	3.8 (3.0;4.5)*	4.0 (3.1;4.9)**	0.5 (-0.3;1.3)*	1.0 (-0.01;2.0)**
Staying in remission	<i>ref</i>	<i>ref</i>	<i>ref</i>	<i>ref</i>
Loosing remission to low disease activity	-4.0 (-4.8;-3.2)*	-4.0 (-5.1;-2.9)**	-1.2 (-2.1;-0.3)*	-0.7 (-1.9;0.5)**

PCS physical component scale score Short form 36 (SF36), MCS mental component scale score SF36, DAS disease activity score, *ref* reference

Data are presented as  $\beta$  estimates (95% CI), representing the estimated difference in change in PCS or MCS score relative to the reference category

## DISCUSSION

In this disease activity targeted treated cohort, lower disease activity was associated with better health related quality of life (HRQoL), both in the physical and mental component scale, although differences in the latter were smaller. This association was independent of the previous disease activity level and related to the final level of disease activity. A change in disease activity resulted in a change in HRQoL. We found that a clinically significant improvement of quality of life (in the physical component scale) was achieved when patients who were in a state of LDA went on to achieve remission.

To date, remission is recommended to be the optimal treatment target in RA patients,<sup>2</sup> but aiming for remission could increase the costs of treatment and the risk of side effects. In patients who have already achieved LDA, it is questionable if a further suppression of disease activity to a level of remission (whether based on a composite score threshold such as <1.6 in the disease activity score or based on the boolean ACR/EULAR remission criteria), also results in a further improvement in quality of life. This we have shown was indeed the case (and reversely, there was a deterioration in HRQoL if disease activity deteriorates from remission to LDA) in this LDA targeted cohort.

Previous studies have shown a cross-sectional correlation between active disease and impaired quality of life measured with generic HRQoL instruments,<sup>10,11</sup> and a dose-response effect of the different disease activity categories.<sup>12,13</sup> In longitudinal analyses over 2 years and over 10 years, it has already been suggested that an improvement in disease activity is associated with better HRQoL.<sup>14,15</sup> This association over a long time



1 span may be influenced by other factors such as damage progression. As disease activity  
2 may fluctuate over time, we focused in our longitudinal analysis on shorter time inter-  
3 vals, and within these shorter time interval we found that improving in DAS and more  
4 specifically achieving remission is associated with improved HRQoL.

5 There are several limitations to our study. A  $DAS < 1.6$  may not denote true remission,<sup>3</sup>  
6 and the distinction with LDA ( $DAS \leq 2.4$ ) is relatively arbitrary. We repeated the analysis  
7 using the ACR/EULAR remission criteria, but here we were limited by the absence of  
8 associated ACR/EULAR low disease activity criteria. Instead, we again compared with  
9 'not in ACR/EULAR remission' with established DAS categories for increased disease  
10 activity. Although according to the ACR/EULAR criteria, less patients were in remission  
11 than when using DAS remission, this did not result in a difference in the association  
12 between disease activity and HRQoL.

13 Second, although the association between disease activity category and HRQoL was  
14 independent of a number of patient characteristics, there might still have been residual  
15 confounding, for example caused by co-morbidity. Therefore, we cannot conclude that  
16 the achievement of remission *causes* patients to have better health related quality of life.  
17 There could be unmeasured patient traits related both to disease activity and HRQoL. A  
18 randomized clinical trial comparing a treatment strategy aiming at LDA with a strategy  
19 aimed at remission using the same therapies would help to answer this question.

20  
21 Although the change in MCS associated with achieving remission from LDA was statisti-  
22 cally significant, it was not clinically significant. However, the mental component was  
23 also less impaired from the outset. The finding that disease activity shows a stronger  
24 relation with the physical than the mental component scale is in line with previous  
25 analyses from this study, where improvement of disease activity was associated with a  
26 smaller improvement of the MCS than the PCS,<sup>16</sup> and data from other cohorts.<sup>17,18</sup> This  
27 may be caused by the fact that in particular the mental component of HRQoL could be  
28 affected by other variables such as pain experience, psychological comorbidity, mental  
29 status, coping strategies and social networks. Also, MCS may depend more on stable  
30 patient traits such as optimism than on disease characteristics, and therefore show less  
31 variation.<sup>19-22</sup>

32  
33 In conclusion, we have shown that a decrease in disease activity in patients with RA is  
34 associated with better HRQoL and that achieving remission after being in LDA is associ-  
35 ated with achieving clinically significant improvement of HRQoL. This may suggest that  
36 remission is the preferred target of treatment and have implications for future (research  
37 on) goal setting in the treatment of RA.

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