# The separate impact of tight control schemes and disease activity on quality of life in patients with early rheumatoid arthritis: results from the CAMERA trials

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## Abstract

### Objective

*To examine in patients with early rheumatoid arthritis (RA) whether quality of life (QoL), independently of disease activity, is affected by tight control treatment strategy schemes.*

### Methods

*In the Computer Assisted Management in Early RA (CAMERA) trials, patients with early RA, disease duration <1 year, no prior use of DMARDs) had been randomised to a methotrexate (MTX)-based tight control strategy or usual care (CAMERA study) or to 10 mg/d prednisone or placebo both added from start to a MTX-based tight control strategy (CAMERA-II study). In either study, randomisation to the more intensive strategy resulted in lower disease activity. To assess QoL, the "Influence of Rheumatic Diseases on General Health and Lifestyle" questionnaire (IRGL) was used. Baseline and 1- and/or 2-year measurements were analysed with regression analyses with the IRGL (sub)scales as outcome variables and treatment strategy and disease activity assessing 28 joints (DAS28) as independent variables, correcting for baseline values of each scale and possible confounders (gender, age, rheumatoid factor status).*

### Results

*There was no clear association between either of the treatment strategies and QoL, but a decrease in DAS28 was associated with improvement in the majority of QoL (sub)scales.*

### Conclusion

*No independent effect of the specific tight control strategies schemes on QoL was found, while there was a clear disease activity related effect. Thus frequent outpatient visits or the inclusion of prednisone in a tight control strategy did not negatively influence QoL.*

**Key words**

early rheumatoid arthritis, tight control, prednisone, glucocorticoids, quality of life, questionnaire, CAMERA (Computer Assisted Management in Early RA)

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## Introduction

Rheumatoid arthritis (RA) is a potentially disabling chronic disease with severe symptoms of pain and stiffness, and eventually joint destruction, deformity and loss of function, challenging quality of life (QoL). Early and intensive treatment may improve outcome. Over the years, there has been growing interest in early arthritis clinics (1), early recognition of RA, and treatment strategies for early RA. The present paradigms for treating (early) RA are tight control (TC) and treat-to-target. TC relates to a treatment strategy with frequent assessments and dose and strategy adjustments tailored to the disease activity of an individual patient aimed at achieving low disease activity or preferably remission within a limited period of time (2). If a treatment aim is a *pre-set* level of low disease activity or remission, a strategy can be described as treat-to-target. Although TC and treat-to-target are similar entities, they are not identical; for instance in our Computer Assisted Management in Early RA (CAMERA) study, both strategies were treat-to-target (remission), but only the intensive strategy with frequent assessments and dose and strategy adjustments was also according to TC. Therapy according to these treatment paradigms has been proven to be more effective compared to conventional strategies (3-7). This was also shown in the CAMERA study (8), that compared the effects of a conventional methotrexate (MTX) based treatment strategy with those of computer assisted MTX based TC strategy. In a consecutive clinical trial, the CAMERA trial II (CAMERA-II), the effects of this TC treatment strategy with addition of 10 mg prednisone daily from start for two years was compared to a MTX-based TC strategy with addition of a daily placebo (9). In both studies the more intensive MTX-based strategies resulted in lower disease activity and higher percentages of patients achieving remission (10).

In the literature, the effects of TC strategies on QoL in RA have been described in one paper only and they were positive (7). However, TC strategies and combination drug schemes (addition of prednisone) may be a burden to patients *e.g.* because the frequent monitoring could affect QoL negatively, as shown in diabetes (11), independently of disease activity. Glucocorticoids (GCs) are frequently used, even in the biologic era (12). Even though they have been proven to be effective symptomatic and disease-modifying drugs (DMARDs) in early RA (13), the (possible) adding of prednisone to the strategy for RA could decrease QoL because of the patients' negative attitude towards this drug (14, 15), and due to psychotropic effects (16). Positive effects of GCs such as euphoria have been described, especially in higher dosages, but also negative effects like depression (17-20). Thus, in RA, both a TC strategy and addition of GCs might directly and indirectly (via disease activity) influence QoL; it is difficult to disentangle these effects in daily practice. Our current design offers the opportunity to examine the independent effects of these treatment strategies.

The aim of this study was to examine in patients with early RA whether quality of life (QoL), independently of disease activity, is affected by a TC treatment strategy scheme, or a TC scheme including prednisone or placebo.

## Patients and methods

*CAMERA and CAMERA II trials*

We reported the design, intervention and main analyses of both the CAMERA-trials in detail elsewhere (8, 9, 10). To summarise, for the CAMERA and the CAMERA II trial, 299 and 236 early RA patients respectively with a disease duration <1 year who fulfilled the 1987 American College of Rheumatology criteria for RA (21) were asked to participate in the two-year randomised, prospective multi-centre strategy trials. All consecutive patients who visited the outpatient clinic of one of the rheumatology departments in the region of Utrecht, the Netherlands, collaborating in the Utrecht Early RA Cohort study group had been asked to participate; patients gave written informed consent before entering the study. Exclusion criteria included previous use of DMARDs, glucocorticoids and elevations of serum liver enzymes.

Participants in the open-label CAMERA trial were randomised into one of two strategy arms, either receiving an intensive treatment strategy with once-monthly visits with medication being adjusted following a tight computer assisted protocol (TC group) or receiving a usual care strategy with three-monthly visits and medication adjustments based on the overall view and opinion of the individual rheumatologist (conventional care at that time, CC). Both arms however were aiming for remission, thus "treat-to-target". The TC MTX-based treatment strategy comprised of a start with 7.5 mg/wk oral MTX, with step-ups of 5 mg/wk to a maximum dose of 30 mg/wk, with daily folic acid (0.5 mg each day, except for the day of MTX intake). In the double-blind treat-to-target CAMERA II trial, both the two strategy arms were similar to the TC group in CAMERA, with one of the two receiving an additional 10 mg/d prednisone (TC+Pred *vs*. TC+Plac); the starting dose MTX was 10 mg, but the step-ups and maximal dose were the same as in CAMERA. The medical research ethics committee of all involved hospitals approved the studies.

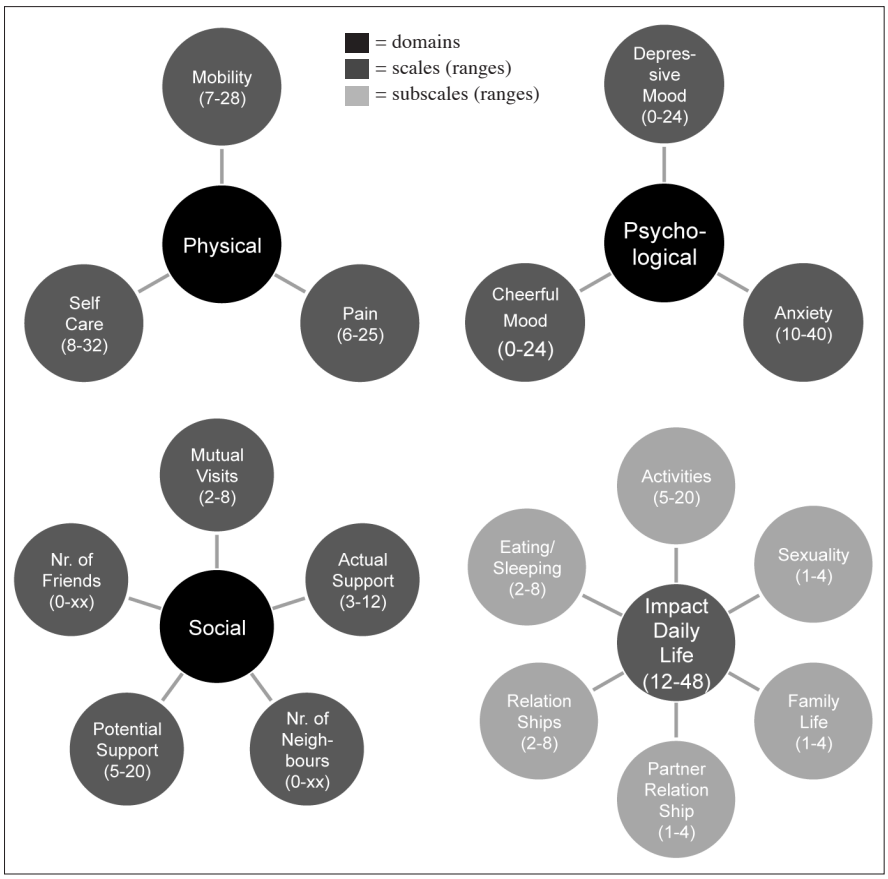


**Fig. 1.** The structure of the questionnaire Influence of Rheumatic Diseases on General Health and Lifestyle (IRGL).
The domains and (sub)scales of the IRGL and their corresponding ranges. The Overall Impact scale (range 10–40) is computed from the subscales Eating/Sleeping, Relationships, Activities and Sexuality from the Impact of the disease on daily life scale.

*Quality of life and disease activity measurements*

The questionnaire "Influence of Rheumatic Diseases on General Health and Lifestyle" (IRGL, a Dutch multidimensional instrument for measuring QoL of patients with RA) was assessed annually during both trials (22). This questionnaire with a total of 68 items with different ranges takes 20 minutes to complete and is based on the Arthritis Impact Measurement Scales (AIMS) (23). The IRGL addresses three domains: Physical function (scales: Mobility, Self care and Pain), Psychological well-being (scales: Depressive mood, Cheerful mood and Anxiety) and Social well-being (scales: number of neighbours who one associates with, number of friends, Potential support, Actual support and Mutual visits). The scale Impact of the rheumatic disease on daily life (Impact on daily life) consisting of the subscales Activities, Sexuality, Eating/Sleeping, Relationships, Partner relationships and Family life is also assessed. An overall impact score of the first four subscales is computed, (see Figure 1). For each (sub)scale score, it applies that the higher the score, the more present the condition, *i.e*. a high score on Mobility reflects good mobility and a high score on Pain reflects severe pain. To calculate the change in IRGL scores between baseline and either 1 or 2 years, IRGL-scores needed to be both present at baseline and at 1 and/or 2 years, leaving 192 of the 299 (64%) and 197 of the 236 (83%) patients in the CAMERA and CAMERA-II trials respectively for evaluation, see Table I. The IRGL scores closest to the yearly time points were used to calculate change scores (= IRGL[scale of interest] at 1 or 2 year *minus* IRGL[scale of interest] at baseline).

Disease activity was measured using the Disease Activity Score assessing 28 joints for swelling and tenderness (DAS28); change scores were calculated over the same time period and in the same way as the IRGL change scores.

*Statistical analyses*

To describe the population, group differences (evaluated within each trial) in means for continuous data were tested for significance using independent samples *t*-tests or Mann Whitney U-tests. For differences in categorical data, Chi-square tests were performed. To study the crude effects within the trail arms on QoL, paired samples t-tests were performed to test changes from baseline within each trial.

To study the effect of treatment strategy on change in each IRGL scale over time (*i.e*. the change over the first year and over 2 years), a linear regression analysis was performed with change scores of IRGL scale as outcome variable and Treatment strategy (TC *vs*. CC in CAMERA and TC+Pred *vs*. TC+Plac in

**Table I.** Baseline characteristics.

| | CAMERA ‡ | | | | | CAMERA-II ‡ | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | Tight Control* | n | Conventional* | *p* | n | Tight Control + Prednisone* | n | Tight Control + Placebo* | *p* |
| Female, n (%) | 96 | 69 (72) | 96 | 63 (66) | 0.35 | 92 | 57 (62) | 105 | 65 (62) | 0.99 |
| Age | 96 | 54.9 (13.5) | 96 | 52.9 (14.3) | 0.34 | 92 | 55.1 (14.0) | 105 | 52.4 (12.9) | 0.17 |
| Rheumatoid factor positive, n (%) | 85 | 60 (63) | 86 | 60 (63) | 0.91 | 80 | 49 (53) | 90 | 67 (64) | 0.07 |
| DAS28 | 95 | 5.6 (1.1) | 95 | 5.6 (1.0) | 0.74 | 91 | 5.8 (1.4) | 103 | 5.6 (1.2) | 0.15 |
| IRGL• (Absolute scale ranges) | | | | | | | | | | |
| Physical function: | | | | | | | | | | |
| Mobility (7-28) | 94 | 19.0 (6.2) | 92 | 19.2 (5.9) | 0.79 | 80 | 20.1 (6.1) | 99 | 20.2 (5.7) | 0.92 |
| Self-care (8-32) | 95 | 24.1 (5.7) | 95 | 24.1 (6.4) | 0.97 | 81 | 24.0 (6.8) | 99 | 25.2 (5.8) | 0.24 |
| Pain (6-25) | 95 | 18.4 (4.0) | 95 | 18.3 (4.2) | 0.85 | 81 | 16.8 (5.6) | 99 | 19.1 (4.0) | 0.00 |
| Psychological well-being: | | | | | | | | | | |
| Depressive mood (0-24) | 95 | 4.6 (3.7) | 94 | 4.6 (3.6) | 0.92 | 83 | 4 (1-6)** | 101 | 4 (1-7)** | 0.22 |
| Cheerful mood (0-24) | 95 | 9.4 (4.2) | 93 | 10.1 (4.6) | 0.31 | 83 | 10.4 (4.7) | 102 | 9.9 (4.6) | 0.49 |
| Anxiety (10-40) | 96 | 19.1 (4.8) | 95 | 19.3 (5.8) | 0.72 | 92 | 18.5 (4.7) | 105 | 19.9 (6.6) | 0.10 |
| Social well-being: | | | | | | | | | | |
| No. of neighbours (0-xx) | 88 | 5 (3-10)** | 84 | 5 (3-10)** | 0.67 | 68 | 7 (4-10)** | 87 | 5 (2-9)** | 0.06 |
| No. of friends (0-xx) | 87 | 9 (5-15** | 83 | 9 (5-14)** | 0.87 | 71 | 6 (4-10)** | 89 | 6 (4-10)** | 0.92 |
| Mutual visits (2-8) | 94 | 5.8 (1.4) | 89 | 5.8 (1.4) | 0.84 | 82 | 5.9 (1.5) | 98 | 5.78 (1.43) | 0.72 |
| Potential support (5-20) | 85 | 16.4 (3.4) | 84 | 15.9 (4.3) | 0.43 | 81 | 17 (15-19.5)** | 97 | 17 (14-20)** | 0.72 |
| Actual support (3-12) | 84 | 6.9 (1.9) | 83 | 6.8 (1.8) | 0.77 | 80 | 6.9 (1.9) | 99 | 6.9 (1.7) | 0.92 |
| Impact on Daily Life (10-40): | | | | | | | | | | |
| Impact on Activities | 83 | 12.5 (3.9) | 85 | 12.2 (3.5) | 0.55 | 86 | 11.0 (3.7) | 99 | 12.3 (4.2) | 0.04 |
| Impact on Sexuality | 79 | 2 (1-2)** | 79 | 1 (1-2)** | 0.64 | 83 | 1.7 (0.8) | 99 | 2.1 (1.1) | 0.03 |
| Impact on Eating/Sleeping | 82 | 3.9 (1.5) | 84 | 4.1 (1.5) | 0.50 | 88 | 3.8 (1.5) | 100 | 4.0 (1.5) | 0.48 |
| Impact on Relationships | 83 | 2 (2-4)** | 87 | 2 (2-4)** | 0.23 | 90 | 2 (2-4)** | 100 | 3 (2-4)** | 0.28 |
| Overall impact† | 84 | 21.2 (6.0) | 86 | 20.7 (5.5) | 0.54 | 87 | 19.5 (5.9) | 100 | 21.3 (7.1) | 0.05 |
| Impact on Partner-relationship | 78 | 1 (1-2)** | 70 | 1 (1-2)** | 0.77 | 74 | 1 (1-2)** | 81 | 2 (1-2)** | 0.04 |
| Impact on Family life | 49 | 1.8 (0.9) | 40 | 2.1 (0.9) | 0.13 | 40 | 1.6 (0.9) | 56 | 2.1 (1.1) | 0.03 |

*mean, Standard deviation, unless stated otherwise; **median, Interquartile range; †Overall impact, comprising of: impact on Activities, on Sexuality, on Eating/Sleeping and on Relationships; •IRGL: Influence of Rheumatic Diseases on General Health and Lifestyle; ‡CAMERA: Computer Assisted Management of Early Rheumatoid Arthritis; CAMERA-II: CAMERA trial 2.

CAMERA-II) as independent variable, both in crude and pooled imputed data. Within the crude data the residuals of change scores were tested, which were reasonably normally distributed. Missing IRGL scores at one and two years were imputed via multiple (5 times) imputation. These one and two year values were both imputed and used as predictor when present for the other time period. Gender, Age, Treatment strategy and the specific IRGL baseline value were entered as predictors in the imputation model.

Regression analyses were performed on the 5 imputed data files resulting in pooled estimates and confidence intervals, reported in Table II.

Two regression models were created per outcome. As independent variables, the first (basic) model included, next to Treatment strategy, Rheumatoid factor status, Gender, Age and the baseline value of the IRGL (sub)scale were analysed, to correct for their effect on the outcome variable.

In the second (final model), to examine the effect of the Treatment strategy on change in each IRGL scale independent from the change in disease activity, the DAS28 crude change score over the same period was added to the basic model.

The statistical programme SPSS version 20.0 was used for all statistical analyses and *p*-values <0.05 were considered statistically significant.

## Results

Baseline characteristics were not statistically significantly different between the 2 treatment strategy arms within each study, with the exception of the IRGL scale Pain and 4 of the 7 impact subscales in CAMERA-II (Table I).

The results of the final regression model analyses are shown in Table II. Only the final model is shown since the significance status (significant or not) of the regression coefficients of the treatment strategies were not different between the basic model excluding DAS28 and the final model including DAS28 as independent variable, except for Family life over 1 year in the CAMERA trial (*i.e.* not significant in the basic model ($p$=0.11), significant in the final model ($p$=0.04).

### *CAMERA*

For the whole CAMERA study population, significant favourable changes from baseline were found for the Physical function and Psychological well-being domains at the 1- or 2-year time points. No significant changes were shown for the domain Social well-being. The scale Impact on daily life showed significant favourable changes for the 2-year time points for the subscales Activities, Eating/Sleeping, Family life and Overall impact but

**Table II.** The effect of treatment strategy and disease activity on quality of life outcomes.

| Dependent | | Selection Final Model | CAMERA | | | CAMERA - II | | |
|---|---|---|---|---|---|---|---|---|
| | | | B | CI | *p* | B | CI | *p* |
| Physical function | | | | | | | | |
| Mobility | Δ 1 yr-BL | Strategy | 0.01 | -0.99 to -1.33 | 0.99 | 0.21 | -1.44 to 1.86 | 0.80 |
| | | Δ DAS28 | -1.32 | -1.76 to -0.89 | <0.001 | -0.77 | -1.24 to -0.29 | 0.002 |
| | Δ 2 yr-BL | Strategy | -0.18 | -1.77 to 1.41 | 0.82 | 0.16 | -1.54 to 1.85 | 0.86 |
| | | Δ DAS28 | -1.03 | -1.59 to -0.46 | <0.001 | -0.69 | -1.24 to -0.13 | 0.02 |
| Self care | Δ 1 yr-BL | Strategy | -0.16 | -1.49 to 1.16 | 0.81 | 0.00 | -1.62 to 1.61 | 1.00 |
| | | Δ DAS28 | -1.26 | -1.69 to -0.84 | <0.001 | -0.41 | -0.89 to 0.06 | 0.09 |
| | Δ 2 yr-BL | Strategy | -0.49 | -2.34 to 1.36 | 0.60 | 1.57 | -0.13 to 3.26 | 0.07 |
| | | Δ DAS28 | -1.27 | -1.92 to -0.61 | <0.001 | -0.20 | -0.76 to 0.36 | 0.49 |
| Pain | Δ 1 yr-BL | Strategy | 0.88 | -0.25 to 2.01 | 0.13 | -0.08 | -1.67 to 1.51 | 0.92 |
| | | Δ DAS28 | 1.67 | 1.31 to 2.04 | <0.001 | 1.02 | 0.55 to 1.48 | <0.001 |
| | Δ 2 yr-BL | Strategy | -0.44 | -1.90 to 1.02 | 0.55 | 0.51 | -1.23 to 2.25 | 0.57 |
| | | Δ DAS28 | 1.59 | 1.07 to 2.10 | <0.001 | 1.16 | 0.61 to 1.71 | <0.001 |
| Psychological well-being | | | | | | | | |
| Depressive mood | Δ 1 yr-BL | Strategy | 0.37 | -0.64 to 1.39 | 0.47 | 0.44 | -0.78 to 1.66 | 0.48 |
| | | Δ DAS28 | 0.70 | 0.37 to 1.03 | <0.001 | 0.77 | 0.42 to 1.12 | <0.001 |
| | Δ 2 yr-BL | Strategy | -0.24 | -1.49 to 1.01 | 0.71 | 0.05 | -1.02 to 1.12 | 0.93 |
| | | Δ DAS28 | 0.52 | 0.08 to 0.97 | 0.02 | 0.67 | 0.34 to 1.01 | <0.001 |
| Cheerful mood | Δ 1 yr-BL | Strategy | -0.59 | -1.65 to 0.48 | 0.28 | -0.59 | -2.13 to 0.94 | 0.45 |
| | | Δ DAS28 | -0.81 | -1.15 to -0.47 | <0.001 | -0.80 | -1.24 to -0.37 | <0.001 |
| | Δ 2 yr-BL | Strategy | -0.64 | -2.21 to 0.92 | 0.42 | 0.33 | -1.14 to 1.79 | 0.66 |
| | | Δ DAS28 | -0.69 | -1.244 to -0.140 | 0.01 | -0.60 | -1.06 to -0.13 | 0.01 |
| Anxiety | Δ 1 yr-BL | Strategy | 0.36 | -0.95 to 1.66 | 0.59 | 0.41 | -1.33 to 2.14 | 0.65 |
| | | Δ DAS28 | 0.99 | 0.57 to 1.41 | <0.001 | 0.60 | 0.09 to 1.11 | 0.02 |
| | Δ 2 yr-BL | Strategy | -0.95 | -2.80 to 0.90 | 0.31 | -0.06 | -1.80 to 1.69 | 0.95 |
| | | Δ DAS28 | 0.93 | 0.26 to 1.59 | 0.01 | 0.34 | -0.20 to 0.87 | 0.22 |
| Social well-being | | | | | | | | |
| No. of neighbours | Δ 1 yr-BL | Strategy | -1.47 | -3.68 to 0.74 | 0.19 | 1.75 | -0.68 to 4.19 | 0.16 |
| | | Δ DAS28 | -0.29 | -1.00 to 0.42 | 0.42 | -0.62 | -1.32 to 0.09 | 0.09 |
| | Δ 2 yr-BL | Strategy | -0.44 | -2.79 to 1.91 | 0.72 | -0.28 | -2.51 to 1.95 | 0.81 |
| | | Δ DAS28 | -0.59 | -1.50 to 0.31 | 0.20 | -0.69 | -1.39 to 0.02 | 0.06 |
| No. of friends | Δ 1 yr-BL | Strategy | -0.48 | -2.99 to 2.03 | 0.71 | -0.90 | -3.29 to 1.48 | 0.46 |
| | | Δ DAS28 | -0.49 | -1.30 to 0.31 | 0.23 | -0.50 | -1.20 to 0.21 | 0.17 |
| | Δ 2 yr-BL | Strategy | 1.14 | -1.53 to 3.81 | 0.40 | -0.90 | -3.19 to 1.38 | 0.44 |
| | | Δ DAS28 | -1.36 | -2.38 to -0.34 | 0.01 | -0.48 | -1.17 to 0.22 | 0.18 |
| Potential support | Δ 1 yr-BL | Strategy | 0.40 | -0.52 to 1.32 | 0.40 | 0.32 | -0.77 to 1.42 | 0.57 |
| | | Δ DAS28 | -0.26 | -0.55 to 0.03 | 0.08 | -0.03 | -0.38 to 0.32 | 0.87 |
| | Δ 2 yr-BL | Strategy | 0.35 | -0.76 to 1.46 | 0.53 | 0.88 | -0.53 to 2.30 | 0.22 |
| | | Δ DAS28 | -0.13 | -0.51 to 0.26 | 0.52 | -0.21 | -0.66 to 0.25 | 0.37 |
| Actual support | Δ 1 yr-BL | Strategy | -0.31 | -0.81 to 0.20 | 0.24 | -0.11 | -0.64 to 0.43 | 0.70 |
| | | Δ DAS28 | -0.09 | -0.26 to 0.08 | 0.28 | 0.04 | -0.12 to 0.20 | 0.63 |
| | Δ 2 yr-BL | Strategy | -0.10 | -0.63 to 0.43 | 0.72 | 0.02 | -0.60 to 0.63 | 0.96 |
| | | Δ DAS28 | -0.17 | -0.36 to 0.03 | 0.09 | -0.06 | -0.25 to 0.13 | 0.54 |
| Mutual visits | Δ 1 yr-BL | Strategy | -0.13 | -0.50 to 0.23 | 0.47 | 0.09 | -0.36 to 0.55 | 0.69 |
| | | Δ DAS28 | -0.08 | -0.20 to 0.04 | 0.17 | 0.01 | -0.13 to 0.15 | 0.89 |
| | Δ 2 yr-BL | Strategy | 0.36 | -0.06 to 0.77 | 0.09 | 0.31 | -0.17 to 0.79 | 0.21 |
| | | Δ DAS28 | -0.17 | -0.27 to 0.04 | 0.13 | -0.01 | -0.17 to 0.14 | 0.87 |
| Impact on Daily Life | | | | | | | | |
| Activities | Δ 1 yr-BL | Strategy | -0.12 | -1.16 to 0.91 | 0.81 | -0.32 | -1.51 to 0.88 | 0.60 |
| | | Δ DAS28 | 0.78 | 0.45 to 1.11 | <0.001 | 0.53 | 0.17 to 0.88 | 0.004 |
| | Δ 2 yr-BL | Strategy | -0.50 | -1.74 to 0.74 | 0.43 | -0.63 | -1.94 to 0.67 | 0.34 |
| | | Δ DAS28 | 0.91 | 0.45 to 1.37 | <0.001 | 0.45 | 0.03 to 0.87 | 0.04 |
| Sexuality | Δ 1 yr-BL | Strategy | -0.04 | -0.33 to 0.26 | 0.80 | 0.04 | -0.24 to 0.32 | 0.77 |
| | | Δ DAS28 | 0.11 | 0.01 to 0.20 | 0.03 | 0.08 | 0.00 to 0.17 | 0.048 |
| | Δ 2 yr-BL | Strategy | -0.27 | -0.58 to 0.04 | 0.08 | -0.10 | -0.40 to 0.20 | 0.52 |
| | | Δ DAS28 | 0.16 | 0.04 to 0.27 | 0.01 | 0.05 | -0.05 to 0.14 | 0.34 |

*(Table II continued)*

| Dependent | | Selection Final Model | CAMERA | | | CAMERA - II | | |
|---|---|---|---|---|---|---|---|---|
| | | | B | CI | *p* | B | CI | *p* |
| Eating/Sleeping | Δ 1 yr-BL | Strategy | 0.18 | -0.30 to 0.65 | 0.47 | -0.10 | -0.52 to 0.32 | 0.65 |
| | | Δ DAS28 | 0.17 | 0.01 to 0.33 | 0.04 | 0.14 | 0.02 to 0.26 | 0.02 |
| | Δ 2 yr-BL | Strategy | -0.10 | -0.55 to 0.35 | 0.67 | -0.17 | -0.64 to 0.30 | 0.48 |
| | | Δ DAS28 | 0.14 | -0.02 to 0.30 | 0.08 | 0.14 | -0.01 to 0.29 | 0.06 |
| Relationships | Δ 1 yr-BL | Strategy | -0.19 | -0.63 to 0.26 | 0.41 | -0.34 | -0.76 to 0.09 | 0.12 |
| | | Δ DAS28 | 0.10 | -0.04 to 0.25 | 0.17 | 0.09 | -0.04 to 0.22 | 0.17 |
| | Δ 2 yr-BL | Strategy | -0.74 | -1.28 to -0.19 | 0.01 | -0.33 | -0.82 to 0.16 | 0.18 |
| | | Δ DAS28 | 0.18 | -0.02 to 0.38 | 0.07 | 0.22 | 0.07 to 0.37 | 0.01 |
| Overall impact | Δ 1 yr-BL | Strategy | -0.08 | -1.81 to 1.65 | 0.93 | -0.78 | -2.53 to 0.97 | 0.38 |
| | | Δ DAS28 | 1.17 | 0.60 to 1.74 | <0.001 | 0.81 | 0.29 to 1.32 | 0.002 |
| | Δ 2 yr-BL | Strategy | -0.93 | -3.29 to 1.43 | 0.44 | -0.93 | -2.97 to 1.11 | 0.37 |
| | | Δ DAS28 | 1.24 | 0.38 to 2.09 | 0.01 | 0.90 | .252 to 1.550 | 0.01 |
| Partner-relationship | Δ 1 yr-BL | Strategy | 0.05 | -0.20 to 0.30 | 0.70 | -0.13 | -0.38 to 0.13 | 0.32 |
| | | Δ DAS28 | 0.04 | -0.05 to 0.12 | 0.40 | 0.07 | -0.01 to 0.15 | 0.09 |
| | Δ 2 yr-BL | Strategy | 0.23 | -0.08 to 0.54 | 0.14 | -0.22 | -0.62 to 0.17 | 0.27 |
| | | Δ DAS28 | 0.06 | -0.06 to 0.18 | 0.35 | 0.09 | -0.04 to 0.21 | 0.18 |
| Family life | Δ 1 yr-BL | Strategy | 0.31 | -.01 to .608 | 0.04 | -0.41 | -0.74 to -0.08 | 0.02 |
| | | Δ DAS28 | 0.09 | -0.01 to 0.19 | 0.08 | 0.04 | -0.05 to 0.13 | 0.37 |
| | Δ 2 yr-BL | Strategy | 0.03 | -0.42 to 0.49 | 0.88 | -0.21 | -0.67 to 0.25 | 0.37 |
| | | Δ DAS28 | 0.17 | 0.01 to 0.33 | 0.04 | 0.04 | -0.09 to 0.18 | 0.53 |

*The final model is a multivariate strategy with treatment Strategy (1: most intensive strategy compared with 0: least intensive strategy), DAS28, rheumatoid factor status, gender, age and the baseline value of each specific IRGL score as independent variables and each IRGL scale per time period as dependent outcome. Missing IRGL score data on 1 and 2 years was multiple (5x) imputed. Data shown are pooled values from the regression analyses.
The interpretation of each score is as follows: the higher the score, the more present the specific condition is. Therefore, a positive B represents an increase and a negative B a decrease of the scale over the respective time period.
*p*-values <0.05 were considered significant.
CAMERA: Computer Assisted Management of Early Rheumatoid Arthritis; B: regression coefficient; CI: 95% Confidence Interval; Yr: year; BL: baseline; CAMERA: tight control MTX-strategy *vs*. usual care; CAMERA-II: tight control MTX-strategy+10mg prednisone *vs*. tight control MTX-strategy+placebo prednisone.

no significant changes for the subscales Sexuality, Relationships and Partner relationships (data not shown).

Between the two treatment strategy arms, there was no significant difference in any of the IRGL change scores for the domains Physical function and Psychological well-being, see Table II. However, the change of disease activity over 1 and over 2 years was significantly related to the change scores on the domains of Physical function (all $p<0.001$) and Psychological well-being (all $p\leq0.02$), *i.e*. a decrease of disease activity was associated with an improvement of QoL.

Treatment strategy and the change of disease activity were not associated with the change in social well-being, with one exception: Decrease of disease activity was related to having more friends ($p=0.01$) over two years.

With respect to impact on daily life, changes in the subscale Relationships over 2 years were in favour of the TC strategy ($p=0.01$), showing less impact of the disease on Relationships compared to CC. The subscale Family life over 1 year ($p=0.04$) showed in the final model more impact of the disease on Family life in the TC strategy group compared to CC. An improvement in disease activity for both time periods was associated to less impact of the disease on almost all subscales of Impact on daily life (all significant values $p\leq0.04$), except for Relationships over 1 and 2 years, Partner-relationships over 1 and 2 years and Family life over 1 year.

*CAMERA-II*

As in the CAMERA cohort, favourable changes from baseline for the whole study population for the Physical function and Psychological well-being domains for the 1- or 2-year time points were statistically significant (data not shown). No significant changes for the Social well-being domain were found, except for a non-favourable change in the scale Potential support over two years. The scale Impact on daily life showed no significant differences for Relationships and Partner relationships over two years. All other subscales and time periods showed favourable significant changes.

Between the two treatment strategy arms, there was no significant difference in any of the IRGL change scores for the domain of Physical function. Disease activity was significantly related to all scales of QoL in this domain, *i.e*. a lowering in DAS28 was related to an improvement in QoL, except for Self care in both time periods. In none of the scales of Psychological well-being significant differences between both treatment strategies were found. A change of disease activity was related to QoL in this domain, except for Anxiety over two years, *i.e*. a lowering in disease activity was related to a favourable change in QoL. In the Social well-

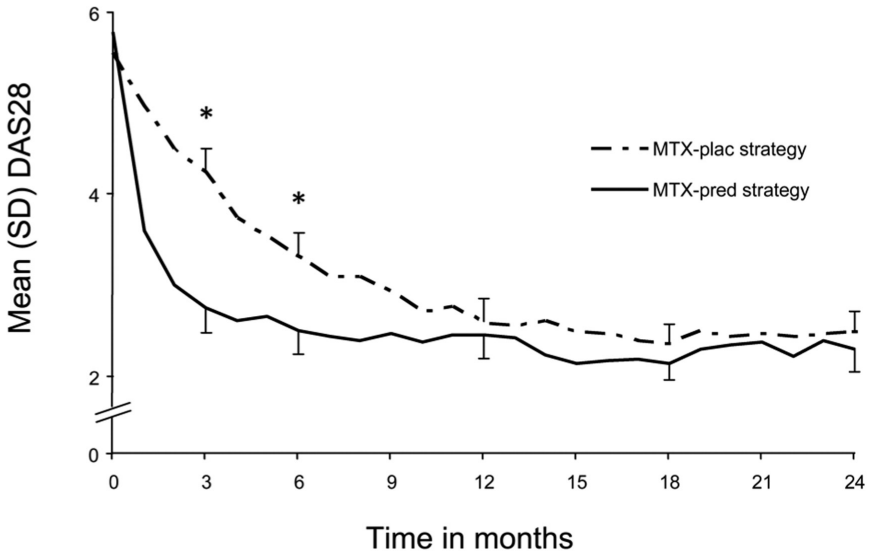


**Fig. 2.** Mean (SD) disease activity score assessing 28 joints (DAS28) in the CAMERA-II trial.
*Statistically significant differences between both treatment arms at these time points, both $p<0.001$.
Effects over time on DAS28: $p<0.001$ between both treatment strategies.
SD: standard deviation; DAS28: Disease Activity Score assessing 28 joints (range, 0 to 9.3 [highest disease activity]); MTX-pred strategy: tight control MTX-based strategy+10 mg prednisone tight control; MTX-plac strategy: tight control MTX-based strategy+placebo prednisone.
Data published: (9).

being domain, neither significant differences were found between the strategy arms, nor was a relation to change of disease activity found. Changes in the subscale Family life over 1 year were significantly in favour of the TC+Pred strategy ($p$=0.02). Changes in disease activity were related to changes in Impact on Activities ($p$=0.004 and $p$=0.04 over 1 and 2 years, respectively), Sexuality (over 1 year, $p$=0.048), Eating/Sleeping (over 1 year, $p$=0.02), Relationships (over 2 years $p$=0.01) and the Overall impact ($p$=0.002 and $p$=0.01 over 1 and 2 years, respectively); a decrease of disease activity was associated with a decrease in Impact.

## Discussion

A reduction in disease activity (DAS28) was associated with improvement on almost all (except for Social well-being) domains of QoL measured through the IRGL.

The very small number (3 regression coefficients) of significant differences between the treatment arms found on the different scales of QoL were not constant over time, indicating a lack of a (long-term) specific strategy effect on QoL. The significant difference in decrease of disease activity between the two treatment arms, in favour of the more intensive strategies, both in CAMERA and CAMERA-II (8, 9) could raise the expectation that QoL would be higher in these more intensive strategy arms. This was not the case. An explanation for this could be that, as a result of the treat-to-target nature of these studies, differences in effects between the strategy arms – which were maximal the first months – diminished over time and were small after 1 and 2 years (see Figure 2), resulting in not statistically significant differences in QoL assessed at yearly intervals. Furthermore, although research suggests that TC according to a standardised protocol results in better outcomes than TC regimes with no such protocol (24), standardised protocols might also negatively impact QoL, *e.g.* because they limit the self-management possibilities of the patient and are associated with frequent outpatient visits and monitoring. Otherwise TC might increase QoL, *e.g.* because it reduces worries and anxiety about the disease course. However, our finding of the very small number of significant differences, which are of little clinical relevance, between the strategy arms found on (different scales of) QoL, conveys the clinically relevant message that our TC strategies did not have a negative or positive effect on QoL. This finding is in support of guidelines recommending to apply treat-to-target strategies, with or without prednisone (25).

Our study has limitations. In the final models many regression analyses were performed, increasing the risk of Type 1 errors. Another limitation is that with the current sample sizes no small differences between the treatment strategy arms could be detected, but great differences probably would have been found. Our results do reinforce earlier findings that improvement in DAS28 also is associated with an improved QoL. To address missing values, a multiple imputation was performed. Analyses with the crude data was very much in line with the imputed data (96% of the regression coefficients significance status (yes/no significant) of the final model with crude and pooled imputed data was the same), the latter being more conservative (*i.e.* less significant differences) and therefore selected as data shown.

The IRGL (especially the Social scales) have not been used and tested widely. Some aspects of the questionnaire were not applicable to all patients (*e.g.* partner relationship and family life) and therefore group sizes differ between the different scales. The social domain may also represent more stable aspects of functioning than the mental well-being, physical functioning and impact domains. The IRGL-scores were obtained annually, which precluded assessing temporarily changes/differences in QoL, *e.g.* if present only during the first few months following the start of the strategy. Both studies involved early RA patients; the effect of treat-to-target strategies on QoL might be different in established RA patients. All outcomes are on group level; individual patients may have experienced significant effects on QoL. Lastly, the specific medication applied for a treat-to-target strategy (*e.g.* glucocorticoids or conventional or biological DMARDs) is important for effects, adverse-effects and therefore QoL. The present study thus only reflects QoL in the specific setting investigated.

## Conclusion

Lowering disease activity was clearly associated with enhanced quality of life, irrespective of how this goal was reached. The present study results are compatible with guidelines recommending to apply treat-to-target and TC strategies.

## Key message

- Lowering disease activity within a TC strategy aiming at remission has a positive effect on QoL;
- The rigorous frequent monitoring visits in a tight control treatment strategy does not impact QoL;
- The addition of prednisone to such a strategy does not impact QoL.

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