Does treat-to-target strategy compared to usual care reduce long-term structural joint damage in rheumatoid arthritis?

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List of abbreviations

ACR	American College of Rheumatology
Anti-CCP	Anti-cyclic citrullinated peptide
BMI	Body Mass Index
CI	Confidence Interval
CRP	C-reactive protein
DAS28	Disease activity score in 28 joints
RDAS	Remission disease activity score
LDAS	Low disease activity score
MDAS	Moderate disease activity score
HDAS	High disease activity score
DMARD	Disease modifying antirheumatic drugs
bDMARD	Biological disease modifying antirheumatic drugs
sDMARD	Synthetic disease modifying antirheumatic drugs
e.g.	For example (in Latin: exempli gratia)
EQ-5D	EuroQol five dimensions
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
HAQ	Health Assessment Questionnaire
HR	Hazard Ratio
HRQOL	Health related quality of life
MST	Medisch Spectrum Twente
MTX	Methotrexate
PATGL	Patient estimate of global status
RA	Rheumatoid Arthritis
RAAD	Rheumatoid Arthritis Articular Damage
Rf	Rheumatoid factor
SD	Standard deviation
SJC	Swollen joint count
TJC	Tender joint count
T2T	Treat-to-Target
VAS	Visual Analogue Scale
vs.	Versus
ZGT	Ziekenhuisgroep Twente

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Vermindert de treat-to-target strategie in vergelijking met de reguliere zorg langdurige structurele gewrichtsschade bij reumatoïde artritis?

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Samenvatting

Achtergrond Het doel van deze studie is om de relatie tussen baseline variabelen en behandelstrategie te evalueren (Treat-to-Target (T2T) of reguliere zorg) met ziekteactiviteit en lange termijn uitkomsten van structurele gewrichtsschade van reumatoïde artritis (RA). T2T bestaat uit strikte behandeldoelstellingen die gericht zijn op een lage RA-ziekteactiviteit (DAS28 ≤2.6) met behulp van synthetische en biologische ziekte veranderende antireumatische geneesmiddelen (DMARD). Een tweede doelstilling is om te analyseren of praktijkvariatie, in de zin van variatie in prestaties van reumatologen, klinische relevante verschillen oplevert in remissie of op de lange termijn.

Methode Deze cohortstudie omvatte 548 patiënten met RA tussen 2006 en 2011 in een regionaal onderwijsziekenhuis in Nederland. Baseline variabelen betreffende eigenschappen van patiënten met RA en behandeling met DMARD's in één van de twee groepen (T2T, reguliere zorg) werden geregistreerd tijdens routinezorg. Ziekteactiviteit werd onderzocht aan de hand van ziekteactiviteit scores (DAS28). Lange termijn uitkomst (Health Assessment Questionnaire (HAQ)) en structurele gewrichtsschade (Rheumatoid Arhtritis Articular Damage (RAAD)) werd na 5 tot 10 jaar beoordeeld tijdens routine poliklinische bezoeken. Onafhankelijke t-testen, Mann Whitney U, $\chi 2$ testen zijn gebruikt om associaties en verschillen tussen baselinevariabelen en uitkomstmaten te vinden. Kaplan-Meier testen zijn gebruikt voor het berekenen van de cumulatieve overlevingskans tot schade. Cox regressie modellen zijn gebruikt om de invloed van tijd en (baseline) variabelen op RAAD-score voor elke groep te bepalen. Variabelen die significant geassocieerd zijn (p<0.05) in univariate analyses zijn gebruikt in het multivariabele model. Resultaten werden uitgedrukt in Hazard ratio (HR) met een 95% betrouwbaarheidsinterval (CI).

Resultaten Er zijn geen grote verschillen tussen de reguliere zorg (n=267) en T2T groep (n=281) bij start diagnose. Meer patiënten stierven in de reguliere zorggroep (8%), maar een gelijk percentage (7%) beëindigde follow-up als gevolg van vroegtijdig drugsvrije remissie. De ziekteactiviteit scores (DAS28) zijn verdeeld in de categorieën: remissie (RDAS ≤2.6), laag (LDAS >2.6-3.2) en medium tot hoog (MDAS – HDAS ≥3.2). De DAS28 is beter na 5 jaar in de T2T groep in vergelijking met de reguliere zorg (RDAS: reguliere zorg 50% vs. T2T 64.3%). De HAQ ondersteunt deze bevindingen met een beter dagelijks functioneren (p<0.01) bij patiënten in remissie (RDAS 0.31, vs. LDAS 0.42, vs. MDAS – HDAS 0.80) uitgedrukt in 'health related quality of life' (HRQOL). De lange termijn uitkomst (RAAD-score) in beide groepen, is niet significant verschillend tussen de reguliere zorg en T2T groep (RAAD=0: reguliere zorg 55% vs. T2T 60%). Er is praktijkvariatie tussen de reumatologen bij het toewijzen van patiënten aan de reguliere zorg of T2T groep. Er zijn ook significant klinische verschillen in de uitkomst van de DAS28 tussen de reumatologen (verschillen in

de aantallen patiënten in remissie). Praktijkvariatie komt ook voor in het verschil in het aantal beoordeling van RAAD-scores. Structurele gewrichtsschade is geassocieerd met de baseline variabelen leeftijd en erosie. Een toename van leeftijd, en de aanwezigheid van erosie bij de start van diagnose hebben een verhoogd risico op gewrichtsschade.

Conclusie T2T-strategie is superieur aan de reguliere zorg in het bereiken van een betere ziekteactiviteit (remissie). Patiënten in remissie, hebben meer kans op een betere lange termijn uitkomst. Structurele gewrichtsschade is niet significant meer aanwezig in de reguliere zorg of T2T groep, maar meer patiënten in de T2T-groep hebben een beter dagelijks functioneren (HAQ). Leeftijd en de aanwezigheid van erosie op moment van diagnose zijn geassocieerd met structurele gewrichtsschade. Reumatologen hebben een voorkeur en beïnvloeden derhalve in welke groep de patiënt wordt behandeld, met klinische verschillen onderling van de DAS28 scores.

Trefwoorden Reumatoïde artritis • Treat-to-Target • praktijkonderzoek • Gewrichtsschade • DAS28

Does the treat-to-target strategy compared to usual care long-term structural joint damage in rheumatoid arthritis?

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Abstract

Background The aim of the study is to assess the relation between baseline variables and treatment strategy (Treat-to-Target strategy (T2T) or usual care) with disease activity and long-term outcome of structural joint damage of rheumatoid arthritis (RA). T2T consist out of a strict treatment targets aiming for low RA disease activity (DAS28 ≤2.6) with the use of synthetic and biological disease modifying antirheumatic drugs (DMARD). A second objective is to analyze whether practice variation, in terms of variation in performance of rheumatologists, results in clinically relevant differences in remission or in long-term outcome.

Methods This cohort study included 548 patients diagnosed with RA between 2006 and 2011 in a regional teaching hospital in the Netherlands. Baseline variables concerning characteristics of patients with RA, and treatment with DMARDs in one of the two groups (T2T, usual care) were recorded during routine care. Disease activity was examined with disease activity scores (DAS28). Long-term outcome (Health Assessment Questionnaire (HAQ)) and structural joint damage (Rheumatoid Arthritis Articular Damage (RAAD)) was assessed after 5 to 10 years during routine outpatient visits. Independent *t* tests, Mann Whitney U, and $\chi 2$ tests are used to find associations and differences between the baseline variables and outcome measurements. Kaplan-Meier tests were used to calculate cumulative survival probability. Cox regression models were used to determine the influence of time and (baseline) variables on RAAD-score for each group. Variables found to be significantly associated ($p<0.05$) in univariate analyses were used into the multivariable model. Results were expressed as Hazard ratios (HR) with a 95% confidence interval (CI).

Results There are no major differences between the usual care (n=267) and T2T group (n=281) at baseline. More patients died in the usual care group (8%), but an equal percentage (7%) ended follow-up because of early drug-free remission. Disease activity scores (DAS28) are divided in the categories: remission (RDAS ≤2.6), low (LDAS >2.6-3.2) and moderate to high (MDAS – HDAS ≥3.2). The DAS28 is better after 5 years in the T2T group compared to the usual care group (RDAS usual care 50% vs. T2T 64.3%). The HAQ supports these findings with a better daily functioning rate ($p<0.01$) in patients who are in remission (RDAS 0.31, vs. LDAS 0.42, vs. MDAS – HDAS 0.80) expressed in health related quality of life (HRQOL). The long-term outcome of the RAAD-score in both groups, is not significant different between the groups (RAAD=0: T2T 60% vs. usual care 55%). There is practice variation between the rheumatologists in allocating patients to the usual care or T2T group. Practice variation also occurs in the difference in amount of assessment of RAAD-scores. Structural joint damage is associated with baseline variables

age and erosion. An increase in age, and the presence of erosion at the onset of diagnosis, give an increasing risk of joint damage.

Conclusions T2T strategy is superior to usual care in achieving faster remission and better disease activity. Patients who are in remission are more likely to have better long-term outcome. Structural joint damage is not significantly more present in the usual care or T2T group, yet more patients in the T2T group do have better functional ability (HAQ). Age and erosion at baseline are associated with structural joint damage. Rheumatologists have a preference and therefore influence in which group the patient is treated, with clinical differences of the DAS28 scores.

Keywords Rheumatoid arthritis • Treat-to-Target • Clinical practice • Articular damage • DAS28

Introduction

An important gap in our knowledge concerns the effects of early interventions on long-term (>5 years) structural joint damage in patients with rheumatoid arthritis (RA) (1,2). The prognosis of RA has improved in the last decades because of the use of synthetic disease modifying antirheumatic drugs (sDMARDs) and biologicals (bDMARDs) (3–5). It was amply demonstrated, that early interventions are effective in reducing radiological joint damage in the first three years in hand – and foot joints (1,6,7). Early initiation of DMARD therapy, that is used in Treat-to-Target (T2T) strategies, aiming for low disease activity or remission of RA after 12 months, reduces radiographic progression (6,8). During T2T quarterly appointments in the first years is advised, in which treatment is adjusted to actual disease activity (DAS28 score). Usually, these appointments are every 2 to 3 months with the rheumatology nurse, supervised by rheumatologists. Based on the judgment of the attending rheumatologist a patient is allocated to the T2T group or treated with usual care group. Usual care treats patients with one or multiple DMARDs, but without pre-defined strict treatment targets as in the T2T strategy. It uses DAS28 as a guideline but without a timeframe, as in the T2T strategy, in which medication is immediately adjusted to the DAS28.

Until now, long-term outcome is commonly measured with questionnaires for well-being and functioning, such as the Health Assessment Questionnaire (HAQ) and the EuroQol five dimensions (EQ-5D) questionnaire (9,10). Limitations of this approach are that these are also influenced by fluctuations of disease activity (11,12). Furthermore, when a destructed joint is replaced with a prosthesis, the outcome may be good, while the result from a perspective of RA treatment is not successful. Another measure of long-term outcome is radiological damage. This is widely used in clinical trials, but is limited to hands and feet. In 2002 the Rheumatoid Arthritis Articular Damage (RAAD) score was developed to quantify structural joint damage in RA (13). The RAAD-score is a clinical count of damage in 35 large and small joints (11). It accounts for orthopedic surgery, does not correlate with actual disease activity, and thus overcomes the limitations of previously used tests.

Long-term disease outcome is determined by many variables, including patient characteristics, treatment strategy, adherence to prescribed medication and individual variation in the response to treatment. Despite guidelines and protocols, there is considerable practice variation between rheumatologists in the treatment of early RA (14). For example, there are differences in guideline adherence and resource utilization (e.g. lab tests and imaging) between rheumatologists (15,16). This raises the question whether such variations can result in relevant differences in long-term outcome.

In this study we assess the complex relations between (i) patient characteristics and treatment strategy (T2T or usual care) of early RA patients, and (ii) disease activity with long-term structural joint damage after 5 to 10 years. A second objective is to analyze (iii) whether practice variation results in clinically relevant differences in remission and/or in long-term outcome.

Methods

Study design and study population

This cohort study included all patients diagnosed with RA between 2006 and 2011 in the regional teaching hospital Ziekenhuisgroep Twente (ZGT) in the Netherlands. In this time-frame patients could be invited to a prospective cohort study with a T2T strategy including protocoled visits by rheumatology nurses. Whether or not patients were included, was based on patients wish or the judgment of the attending rheumatologist. This judgment was presumably influenced by factors such as the certainty of the diagnosis, comorbidity, and if a strict T2T protocol was suited to a particular patients' need. However, patients not included in the T2T cohort were treated according to their clinical diagnosis with standard treatments for RA ("usual care").

For this study we used as inclusion criteria: clinical diagnosis of RA between January 1, 2006 and December 31, 2011 in the ZGT. Exclusion criteria were: initial treatment and follow-up in another hospital and rejection of clinical diagnosis of RA during follow-up. End of follow-up was obtained by review of electronic patients records and defined as: death, drug-free remission or other reasons such as continuation of care or care in another hospital.

Ethics

The medical ethics committee of the Medisch Spectrum Twente (MST), Enschede exempt this study from ethical approval, in accordance with Dutch law of Medical Research Involving Human Subjects Act, because the T2T patients have been informed in the past concerning their treatment data being used for research and no action or behavior is imposed on participating patients (protocol and informed consent in appendix 1). Patients treated with usual care were not asked to fill in an informed consent form because no particularities were applied in their treatment. Also the advisory committee on local feasibility scientific research (ALU) of the ZGT gave approval for this study (confirmation of METC and ALU in appendix 3).

Treatment profiles

Patients were allocated to the usual care or T2T group. No reason was indicated in the records for allocating a patient to the usual care or T2T group. The T2T strategy is recommended by the European League Against Rheumatism (EULAR) for management of RA with synthetic DMARDs and biologicals (17). The T2T strategy entails quarterly appointments in the first years, in which treatment is adjusted to actual disease activity score (DAS28). In the ZGT, these appointments are every 2 to 3 months with the rheumatology nurse, supervised by the rheumatologists. The T2T protocol comprised a start with methotrexate 15 mg per week, with dose increments or addition of sulphasalazine according to disease activity (DAS28). bDMARDs could be added with sustained disease activity after 6 months, which at the time was quite early compared to usual care, and prednis(ol)on was used according to the rheumatologists judgment.

Usual care is traditional routine care without a strict protocol. Patients in this group are treated with one or multiple DMARDs, but without pre-defined strict treatment targets as in the T2T strategy. It uses DAS28 as a guideline but without a timeframe, as in the T2T strategy, in which medication is immediately adjusted to the DAS28. Also the use of biologicals is less strict which may result in a longer time to start a first bDMARD. In the usual care group rheumatologists were of course aware of the T2T protocol, but made personal choices according to their best judgment of the patients needs.

Outcome

Baseline

Baseline characteristics including ACR 2010 criteria, DAS28 measurements, DMARD use and HAQ are routinely recorded in the hospital information system. All data were exported from the electronic patient records to an anonymized database. Baseline variables made at the time of diagnosis, between the years 2006 and 2011, were completed by the nurses and rheumatologists in the hospital information system. These variables have been collected until end follow-up, with end date May 1, 2017.

Clinical parameters are variables with factual data such as age and date of assessment. Laboratory measurements include: serology (rheumatoid factor (Rf) and anti-cyclic citrullinated peptide (anti-CCP)), acute phase reactants (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)). The ACR/EULAR 2010 score exists of multiple components (3): affected joints, duration of symptoms (<6 weeks, >6 weeks), serology and acute phase reactants. All clinical and laboratory variables are measured directly at start diagnosis, except for anti-CCP (measured since 2006).

Primary outcome: Long-term: RAAD and HAQ

Long-term structural joint damage after 5 to 10 years is assessed with the RAAD-score. The RAAD is a scoring method integrated in the electronic patient record (EPR) system of the ZGT since 2014. The RAAD is a reliable and valid tool to measure irreversible damage in 35 joints (13). In the RAAD-score each joint is scored on a 3-point scale (0: no irreversible damage, 1: partly damaged, 2: severe damage). The maximum total score is 70, with higher scores indicating more damage (13) (Figure 1).

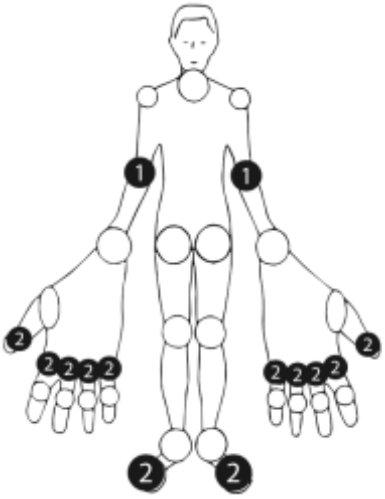

Figure 1 RAAD scoring system

Another long-term outcome is evaluated with the HAQ. The HAQ is proven to be a valid and reliable instrument to assess health related quality of life (HRQOL) (18). On a 4-point scale the questions of the HAQ are divided in 9 categories: dressing, arising, eating, walking, hygiene, reach, grip, activity, satisfaction (19). Experienced difficulties in the past week were scored by the patient on a scale of 0 to 3 (0: without difficulty, 1: with some difficulty, 2: with much difficulty, 3: unable to do).

Intermediate outcome: DAS28

The intermediate outcome measured in disease activity was assessed in 28 joints by the DAS28, consisting out of four elements: tender joint count (TJC), swollen joint count (SJC), ESR/CRP, and patient estimate of global status (PATGL) on a VAS (20,21). The DAS28 is an intermediate outcome to evaluate whether disease activity is a predictor for the long-term outcome. DAS28 is a validated instrument to measure underlying inflammation for use in RA clinical trials and individual monitoring of patients (20). For this analysis the mean DAS28 score for each patient during the first 5 years was used to allocate patients in one of three categories: remission (RDAS ≤2.6), low (LDAS >2.6-3.2), moderate to high (MDAS – HDAS ≥3.2) disease activity (10,22). DAS28 scores assessed within the first three weeks after diagnosis are excluded because of high and distortionary DAS28 scores due to the early stage of DMARD treatment.

Practice variation

To assess the influence of possible practice variation on the intermediate and long-term outcome variables, separate analyses per rheumatologist were performed. Rheumatologists who treated less than 15 patients between 2006 and 2011 were excluded from these analyses. Small numbers of patients were due to rheumatologists being no longer active as rheumatologists, or because they were a new member of the team, that limits comparability with other rheumatologists based on their population size.

Statistical analysis

In the baseline table descriptive statistics for categorical variables were reported as frequencies (n), percentages (%). Quantitative variables were reported with means and standard deviations. Independent *t* tests and ANOVA are used to find differences between normally distributed variables (and categorical variables). For not normally distributed variables, median and interquartile range (IQR) is reported. Mann Whitney U test was used to test for differences between not normally distributed variables. Differences in categorical variables are tested with the $\chi 2$ tests. Kaplan-Meier tests were used to calculate cumulative survival probability per group. Cox regression models were used to estimate the influence of time and (baseline) patient characteristics on RAAD-score. Variables found to be significantly associated (cut-off point: $p<0.15$) in univariate analyses were used into the multivariable model. Results of the multivariable model were expressed as Hazard ratios (HR) with a 95% confidence interval (CI): a p-value of less 0.05 is considered significant. Statistical analyzes were carried out with SPSS version 23, Inc. Chicago Illinois.

Results

Patient characteristics (and treatment strategy)

Table 1 summarizes baseline patient characteristics and DMARD use in the first 5 years of both groups. From the 548 RA patients included, 267 (49%) patients are in the usual care group and 281 (51%) in the T2T group. Patients in the usual care group have a mean follow-up of 7.6 years, in the T2T group 8.9 years (appendix 2, figure 6).

Table 1 RA patient characteristics at baseline (2006 – 2011), DMARD use after first 5 years

Characteristics	Usual care (*n*=267)	Treat-to-Target (*n*=281)	*P*
Female, sex, *n* (%)	170 (63.7%)	169 (60.1%)	
Age, years, mean ±SD	61.1 ±15.6	59.3 ±14.4	
ESR (mm/h)[1], median (IQR)	29 (16 – 47)	28 (15 – 46)	
CRP, mg/L[2], median (IQR)	13 (5 – 42)	14 (5 – 34)	
ACR 2010 score, ≥ 6 (%)	152 (56.9%)	155 (55.2%)	
Anti-CCP[3] positive, *n* (%)	78 (53.1%)	75 (48.1%)	
Rf-positive[4], *n* (%)	153 (58.2%)	147 (52.9%)	
Erosions[5], *n* (%)	42 (16.5%)	53 (18.9%)	
BMI[6], kg/m^2, mean ±SD	27.2 ±4.8	26.4 ±4.7	<0.01
DAS28 (t=0)[7], mean ±SD	3.4 (±1.7)	4.9 (±1.3)	
Affected joints, *n* (%)			
1 medium-large joint	0 (0%)	4 (1.4%)	<0.01
1-3 small joints	76 (28.5%)	36 (12.8%)	
2-10 medium-large joints	22 (8.2%)	37 (13.2%)	
4-10 small joints	107 (40.1%)	128 (45.6%)	
>10 joints (at least 1 small joint)	62 (23.2%)	76 (27.0%)	
Smoking status[8], *n* (%)			
Smoking	74 (30.7%)	91 (34.9%)	
Quit smoking (before RA diagnosis)	81 (33.6%)	86 (33.0%)	
Never smoked	86 (35.7%)	84 (32.2%)	
Quit during study	10 (4.1%)	19 (6.8%)	
DMARD[9], *n* (%)			
MTX	200 (74.9%)	279 (99.3%)	<0.01
sDMARD	174 (65.2%)	183 (65.1%)	<0.01
bDMARD	48 (18.0%)	87 (31.0%)	
Predis(ol)on	97 (36.3%)	81 (28.8%)	
Prednis(ol)on before RA diagnosis, *n* (%)	38 (14.2%)	13 (4.6%)	<0.01

ESR erythrocyte sedimentation rate, *CRP* C-reactive protein, anti-cyclic citrullinated peptide, *ACR* American College of Rheumatology, *Rf* rheumatoid factor, *Anti-CCP* Anti cyclic citrullinated peptides*, BMI* body mass index, *DAS28* disease activity score in 28 joints*, MTX* methotrexate, *sDMARD* synthetic disease modifying antirheumatic drugs, *bDMARD* biological disease modifying antirheumatic drugs, *Pred* Prednis(ol)on.

Missing

[1] ESR: 7 (4 UC, 3 T2T)
[2] CRP: 19 (15 UC, 4 T2T)
[3] Anti-CCP: 245 (120 UC, 125 T2T)
[4] Rf: 7 (4 UC, 3 T2T)
[5] Erosions: 12 (12 UC, 0 T2T)
[6] BMI: 90 (68 UC, 22 T2T)
[7] DAS28: 186 (167 UC, 19 T2T)
[8] Smoking status: 46 (26 UC, 20 T2T)
[9] DMARD: 14 (13 UC, 1 T2T)

There are some small differences in patient characteristics between the two groups, such as the first DAS28 and affected joints. The DAS28 is higher in the T2T group (3.4 vs. 4.9). There were more patients with one affected large joint in the usual care group, and more patients with 4 – 10 small joints in the T2T group (p<0.01). In the usual care group more patients (14.2% vs. 4.6%) received prednis(ol)one before RA diagnosis compared to the T2T group (p<0.01). During the entire study period, the majority of patients (87.4%) were treated with MTX. More patients in the T2T group were treated with MTX compared to the usual care group (74.9% vs. 99.3%; p<0.01). Patients in the T2T group also received more bDMARDs (18% vs. 31%; p<0.01), an expected result from the T2T protocol.

Treatment strategy and disease activity in first 5 years

Intermediate outcome: DAS28

A total of 420 patients (usual care: 139, T2T: 281) had DAS28 recorded during the first 5 years after diagnosis; with all 128 missing's in the in the usual care group. After excluding patients with DAS28 within the first 3 weeks, 382 patients remained (usual care: 102, T2T: 280, missing: 166). On average the DAS28 was recorded 4 times per patient in the usual care group, against 19 times in the T2T group between year 1 and 5. As reported in table 1, the first DAS28 is different between the groups with a mean of 3.4 in the usual care group and 4.9 T2T group (95% confidence interval [CI] usual care: 3.1 – 3.8, vs. T2T: 4.7 – 5.0; p<0.01).

Table 2 DAS28 in the first 5 years per group

	Usual care (*n*=102)	**Treat-to-Target (*n*=280)**	***P***
DAS28, *n* (%)			<0.05
RDAS	52 (51.0%)	166 (59.3%)	
LDAS	20 (19.6%)	64 (22.8%)	
MDAS – HDAS	30 (29.4%)	50 (17.9%)	

DAS28 disease activity score in 28 joints: *RDAS* remission disease activity score, *LDAS* low disease activity score, *MDAS* moderate disease activity score, *HDAS* high disease activity score

Missing

[1] DAS28: 166 (165 UC, 1 T2T)

Table 2 reports the differences in DAS28 score between the usual care and T2T group divided in categories (RDAS, LDAS, MDAS – HDAS). Overall 57% (n=218) of the patients with DAS28 scores were in remission over the entire 5-year follow-up. In the first five years, more patients in the T2T group were in remission (51% vs. 59.3%) but also more low disease activity scores (19.6% vs. 22.8%; p<0.05). In the usual care group, more patients had higher DAS28 scores (MDAS – HDAS: 29.4% vs. 17.9%) compared to the T2T group.

Figure 2 illustrates the time (in years) to achieve remission (DAS28 ≤2.6) for the usual care and T2T group. The T2T groups starts from a difficult position with higher DAS28 scores higher at the start (t=0). After year 0, the line drops steeper for the T2T group during the period of 5 years. In the usual care group the mean time to reach remission is 1.7 years, versus 0.9 years in the T2T group (95% CI usual care: 1.4 – 2.0, vs. T2T: 0.7 – 1.0). Patients in the T2T group reach earlier remission compared to usual care (p<0.01).

As table 2 and figure 2 illustrate, the T2T group reaches faster remission, we should however consider there are more patients in the usual care group lost to follow-up because of being in remission, which will be discussed in paragraph 3, figure 3 and appendix 2, figure 7.

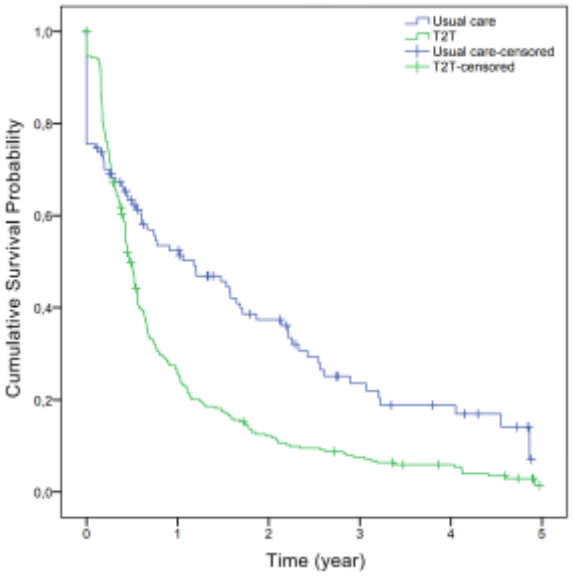

Figure 2 Kaplan-Meier overall survival of RA patients in the usual care and T2T group achieving remission during first 5 years

Treatment strategy and long-term outcome

The effects between the usual care and T2T group are assessed in this chapter based on the long-term outcome variables: RAAD and HAQ. Because not all patient were assessed with RAAD or HAQ-scores, the analysis only uses patients who contain RAAD or HAQ-scores.

Treatment strategy and long-term outcome: RAAD-score

As expected in this study of "real-life practice cohorts", some patients were longer in the follow-up than others, and since the RAAD-score was added as an outcome measure in 2014, it could not be assessed from all patients. The flowchart in figure 3 illustrates how many patients are eligible for RAAD-scores in each group (usual care, T2T), and how many actually contain RAAD-scores. In the usual care group, 144 patients quit during the follow-up period (January 1, 2006 – May 1, 2017) because of multiple reasons (deceased, remission, other). A smaller amount of patients (33%) quit from the study in the T2T group because of similar reasons as in the usual care group (54%).

Notably, more patients in the usual care group died compared to the T2T group (23% vs. 15%; $p<0.01$). There were also more patients in the usual care group (19% vs. 12%) who ended the follow-up because of early drug-free remission ($p<0.01$). Overall 237 patients were lost for follow up, 103 patients died, 86 patients were in remission, 13 patients moved, and 35 patients had other reasons; 311 patients are still in follow-up at May 1, 2017.

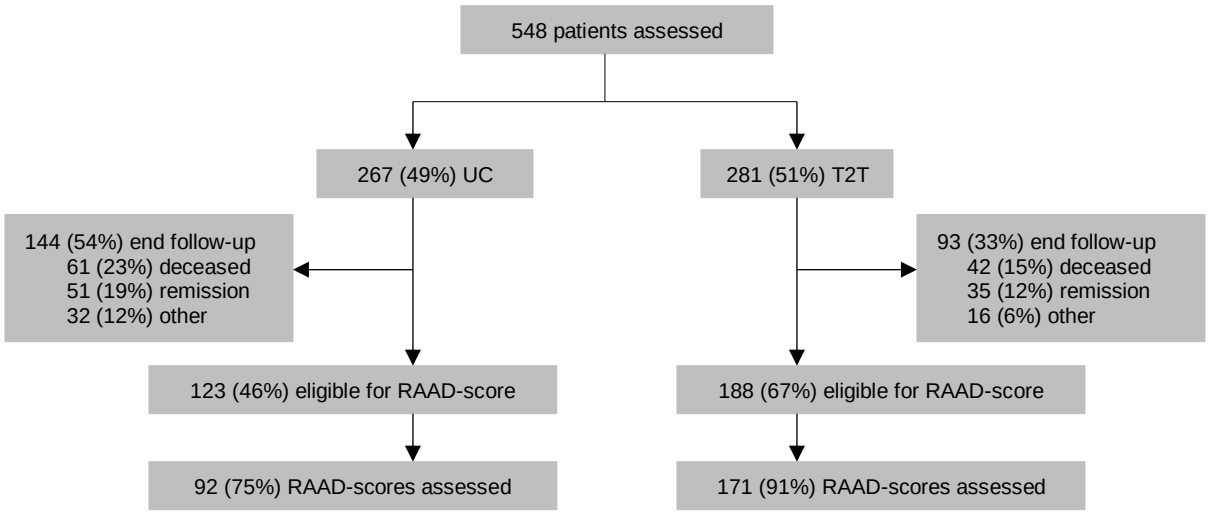

Figure 3 Flowchart

The patients with RAAD-scores (usual care group: 92, T2T: 171) are included for analysis. The number of RAAD-scores is spread over 4 years (2014 – 2017), with a maximum of 4 RAAD-scores per patient. The most recent assessed RAAD-score is used for this analysis: considering the last RAAD-score is the actual irreversible joint damage.

RAAD: Usual care versus Treat-to-Target

To assess whether patients with RAAD-scores differ at baseline between the usual care and T2T group, a second baseline table is created (table 3). There are some differences in patient characteristics between the two groups, such as DAS28, affected joints, MTX and prednis(ol)one use before diagnosis. Patients in the T2T group start (t=0) with a higher DAS28 compared to the usual care group (3.5 vs. 4.9). There were more patients with one affected large joint in the usual care group, and more patients with 4 – 10 small joints in the T2T group (p<0.01). All patients in the T2T group used MTX, versus a smaller amount of patients in the usual care group (94.6% vs. 100%; p<0.01). In the usual care group more patients (15.2% vs. 4.1%) received prednis(ol)one before RA diagnosis (p<0.01).

Table 3 Baseline (2006 – 2011) characteristics of only RA patients with a RAAD-score

Characteristics	**Usual care (*n*=92)**	**Treat-to-Target (*n*=171)**	***P***
Female, sex, *n* (%)	65 (70.7%)	100 (58.5%)	
Age, years, mean ±SD	55.0 ±13.6	56.3 ±13.5	
ESR (mm/h)[1], median (IQR)	29 (17 – 43)	26 (14 – 44)	
CRP, mg/L[2], median (IQR)	13 (5 – 36)	14 (3 – 34)	
ACR 2010 score, ≥ 6 (%)	59 (64.1%)	99 (57.9%)	
Anti-CCP[3] positive, *n* (%)	28 (54.9%)	50 (54.9%)	
RF-positive[4], *n* (%)	57 (62.6%)	95 (55.9%)	
Erosions[5], *n* (%)	18 (19.8%)	30 (17.5%)	
BMI[6], kg/m^2, mean ±SD	27.2 ±5.1	26.2 ±4.0	
DAS28 (t=0)[7], mean ±SD	3.5 (±1.8)	4.9 (±1.3)	<0.01
Affected joints, *n* (%)			<0.01
1 medium-large joint	0 (0%)	2 (1%)	
1-3 small joints	26 (28.3%)	21 (12%)	
2-10 medium-large joints	7 (7.6%)	23 (14%)	
4-10 small joints	40 (43.5%)	83 (48%)	
>10 joints (at least 1 small joint)	19 (20.7%)	42 (25%)	
Smoking status[8], *n* (%)			
Smoking (currently)	26 (30.6%)	52 (31.9%)	
Quit smoking (before study)	29 (34.1%)	60 (36.8%)	
Never smoked	30 (35.3%)	51 (31.3%)	
Quit during study	6 (7.1%)	14 (8.5%)	
DMARD, *n* (%)			
MTX	87 (94.6%)	171 (100%)	<0.01
s-DMARD	73 (79.3%)	120 (70.2%)	
b-DMARD	38 (41.3%)	70 (40.9%)	
Predis(ol)on	37 (40.2%)	50 (29.2%)	
Prednis(ol)on before RA diagnosis, *n* (%)	14 (15.2%)	7 (4.1%)	<0.01

ESR erythrocyte sedimentation rate, *CRP* C-reactive protein, anti-cyclic citrullinated peptide, *ACR* American College of Rheumatology, *Anti-CCP* Anti cyclic citrullinated peptides, *Rf* rheumatoid factor, *BMI* body mass index, *DAS28* disease activity score in 28 joints, *MTX* methotrexate, *sDMARD* synthetic disease modifying antirheumatic drugs, *bDMARD* biological disease modifying antirheumatic drugs, *Pred* Prednis(ol)on.

Missing

[1] ESR: 3 (2 UC, 1 T2T)
[2] CRP: 5 (3 UC, 2 T2T)
[3] Anti-CCP: 141 (41 UC, 80 T2T)
[4] Rf: 4 (2 UC, 2 T2T)
[5] Erosions: 1 (1 UC, 0 T2T)
[6] BMI: 12 (5 UC, 7 T2T)
[7] DAS28: 41 (29 UC, 12 T2T)
[8] Smoking status: 15 (7 UC, 8 T2T)

Another comparison between the two groups with RAAD-scores is made based on outcome variables (table 4). The DAS28 reports the mean disease activity after 5-years categorized in groups, the HAQ and RAAD are outcome measures after 5 to 10 years. The RAAD-score is categorized in three categories (0, 1 – 4 and ≥5) to illustrate the variety and to divide patients by severity of joint damage. It is evident that T2T results in better suppression of disease activity (RDAS: 50% vs. 64.3%; p<0.01).

As may be expected with the low disease activity over the first 5 years, the outcome in terms of HAQ is better in the T2T group. For the HAQ, there is a higher functional ability in the T2T group compared to the usual care group (0.56 vs. 0.39; p<0.05). However, for the RAAD-score there are no significant differences between the two groups.

Table 4 DAS28 mean after first 5 years, HAQ and RAAD after 5 – 10 years for patients with RAAD-scores

Characteristics	**Usual care (*n*=92)**	**Treat-to-Target (*n*=171)**	***P***
DAS28[1]			
RDAS	34 (50.0%)	110 (64.3%)	<0.01
LDAS	12 (17.6%)	42 (24.6%)	
MDAS – HDAS	22 (32.4%)	19 (11.1%)	
HAQ[2], mean ±SD	0.55 (±0.56)	0.37 (±0.44)	<0.05
RAAD, *n* (%)			
0	51 (55.4%)	102 (59.6%)	
1-4	29 (31.5%)	57 (33.3%)	
≥5	12 (13.0%)	12 (7.0%)	

DAS28 disease activity score in 28 joints: *RDAS* remission disease activity score, *LDAS* low disease activity score, *MDAS* moderate disease activity score, *HDAS* high disease activity score, *HAQ* Health Assessment Questionnaire, *RAAD* Rheumatoid Arthritis Articular Damage score.

Missing

[1] DAS28: 24 (24 UC, 0 T2T) [2] HAQ: 59 (23 UC, 36 T2T)

Treatment strategy and long-term outcome: HAQ-score

The HAQ-score is a long-term outcome that complements the short-term outcome of the DAS28 with subjective data of a questionnaire filled in by the patient. A total of 204 patients were assessed for HAQ-scores. Patients in the usual care group (n=69) have a mean HAQ-score of 0.55 (±0.56) compared to a lower mean HAQ-score of 0.37 (±0.45) in the T2T group (n=135) (p<0.05). The HAQ-scores improved between the first and second HAQ-score with 30% in the usual care group (0.63 vs. 0.44), and in the T2T group with 57% (0.44 vs. 0.19).

Figure 4 illustrates the time to a patient achieving a HAQ-score below the cut-off point of 0.3 (0=no functional impairment, 3=complete impairment). The mean time patients in the T2T group reach a low HAQ-score is 7.4 years, versus 8.4 years in the usual care group (p<0.01). We should take into account that patients in the T2T group also are earlier assessed for HAQ-scores (appendix 2, figure 7: usual care 7.3 years vs. T2T 6.7 years).

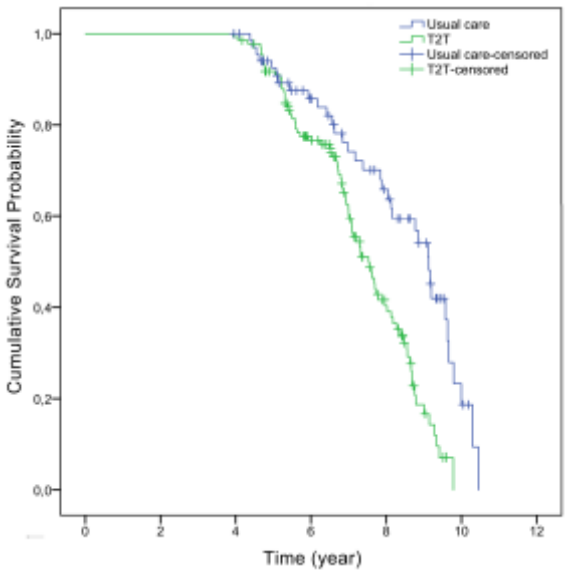

Figure 4 Kaplan-Meier overall survival of RA patients in the usual care and T2T group achieving 0.3 HAQ-score

Interrelations between intermediate and long-term outcome variables

This extra section examines the relation between the outcome variables in previous paragraphs because we know from previous studies there is an association between the DAS28 and HAQ, also reported in table 5. Due to this fact, it is interesting to analyze whether the same association occurs between the DAS28 and RAAD This provides us an in-depth analysis of the outcome variables.

From the patients with HAQ-scores (*n*=204), patients with lower DAS28-scores (RDAS) have better HAQ-scores compared to low-, moderate-, or high DAS28 scores (0.31 vs. 0.42 vs. 0.80) (p<0.01). The situation in DAS28-scores, where the lowest score contain better functional ability, does not apply for patients with low RAAD-scores (RAAD=0 0.38). Patients with lower RAAD-scores (RAAD<4) indicate to have better functional ability (0.38, ±SD 0.52 and 0.37, ±SD 0.38) compared to patients with higher RAAD-scores ≥5 (0.78, ±SD 0.51) (p<0.01).

Table 5 Comparison of HAQ scores between short-term and long-term outcome measurements

		HAQ	***P***
	***n*(%)**	**Mean, ±SD**	
DAS28[1]			
RDAS	109 (57.4%)	0.31 (±0.41)	<0.01
LDAS	46 (24.1%)	0.42 (±0.41)	
MDAS – HDAS	36 (18.8%)	0.80 (±0.59)	
RAAD[2]			<0.01
0	101 (54.9%)	0.38 (±0.52)	
1 – 4	64 (34.8%)	0.37 (±0.38)	
≥5	19 (10.3%)	0.78 (±0.51)	

HAQ Health Assessment Questionnaire, *DAS28* disease activity score in 28 joints: *RDAS* remission disease activity score, *LDAS* low disease activity score, *MDAS* moderate disease activity score, *HDAS* high disease activity score, *RAAD* Rheumatoid Arthritis Articular Damage score.

Sub-analyses (*n*=239) examined interrelationships between disease activity (DAS28) and structural joint damage (RAAD). Apart from the strategy chosen by the rheumatologists, table 6 illustrates that disease remission in the first 5 years is associated with reduced long-term joint damage. A large proportion (65.3%) of the patients in remission have no joint damage (RAAD=0). However, from the patients in remission, still 4.9% contains high RAAD-scores (≥5) (p<0.01). Table 6 illustrates the same relation between DAS28 and RAAD, as the relation between DAS28 and HAQ.

Table 6 Interrelationship RAAD and DAS28

	RAAD			**Total**	***P***
	0	**1 – 4**	**≥5**		
DAS28 mean 1-5, *n*(%)					
RDAS	94 (65.3%)	43 (29.9%)	7 (4.9%)	144	
LDAS	29 (53.7%)	21 (38.9%)	4 (7.4%)	54	
MDAS – HDAS	15 (36.6%)	16 (39.0%)	10 (24.4%)	41	
Total	138	80	21	239	<0.01

RAAD Rheumatoid Arthritis Articular Damage score. *RDAS* remission disease activity score, *LDAS* low disease activity score, *MDAS* moderate disease activity score, *HDAS* high disease activity score.

RAAD: structural joint damage versus no structural joint damage

Patients differ significantly between the usual care and T2T group on several baseline variables in table 3. When we regroup these patients in groups of 'no damage' (*n*=153) and 'damage' (*n*=110), by combining category: RAAD 1 – 4 and category: RAAD ≥5, it also evaluates the differences at baseline based on the outcome variable (table 7).

The baseline variables, age, ESR, CRP, erosion and first DAS28 significantly differ between patients with no damage and patients with damage. Patients with no structural joint damage are younger (53.8 vs. 58.7), have lower ESR (22.5 vs. 32) and CRP (10 vs. 17), less erosion (11.8% vs. 27.5%) and a lower DAS28 at baseline (4.3 vs. 4.7).

Table 7 Baseline (2006 – 2011) characteristics of RA patients divided by RAAD-score

	RAAD		***P***
Characteristics	**0 (*n*=153)**	**≥1 (*n*=110)**	
Female, sex, *n* (%)	96 (62.7%)	69 (62.7%)	
Age, years, mean ±SD	53.8 ±12.4	58.7 ±14.5	<0.01
ESR (mm/h)[1], median (IQR)	22.5 (12 – 41)	32 (18 – 46)	<0.01
CRP, mg/L[2], median (IQR)	10 (3 – 26)	17 (6 – 43)	<0.05
ACR 2010 score, ≥ 6 (%)	90 (58.8%)	68 (61.8%)	
Anti-CCP[3] positive, *n* (%)	42 (51.9%)	36 (59.0%)	
RF-positive[4], *n* (%)	90 (59.6%)	62 (56.4%)	
Erosions[5], *n* (%)	18 (11.8%)	30 (27.5%)	<0.01
BMI[6], kg/m^2, mean ±SD	26.4 ±4.2	26.7 ±4.7	
DAS28 (t=0)[7], mean ±SD	4.3 ±1.7	4.7 ±1.3	<0.05
Affected joints, *n* (%)			
1 medium-large joint	2 (1.3%)	0 (0%)	
1-3 small joints	32 (20.9%)	15 (13.6%)	
2-10 medium-large joints	14 (9.2%)	16 (14.5%)	
4-10 small joints	69 (45.1%)	54 (49.1%)	
>10 joints (at least 1 small joint)	36 (23.5%)	25 (22.7%)	
Smoking status[8], *n* (%)			
Smoking (currently)	42 (29.4%)	36 (34.4%)	
Quit smoking (before study)	54 (37.8%)	35 (33.3%)	
Never smoked	47 (32.9%)	34 (32.4%)	
Quit during study	11 (7.7%)	9 (8.6%)	
DMARD, *n* (%)			
MTX	150 (98.0%)	108 (98.2%)	
s-DMARD	117 (76.5%)	76 (69.1%)	
b-DMARD	59 (38.6%)	49 (44.5%)	
Predis(ol)on	48 (31.4%)	39 (35.5%)	
Prednis(ol)on before RA diagnosis, *n* (%)	9 (5.9%)	12 (10.9%)	

ESR erythrocyte sedimentation rate, *CRP* C-reactive protein, anti-cyclic citrullinated peptide, *ACR* American College of Rheumatology, *Anti-CCP* Anti cyclic citrullinated peptides, *Rf* rheumatoid factor, *BMI* body mass index, *DAS28* disease activity score in 28 joints, *MTX* methotrexate, *sDMARD* synthetic disease modifying antirheumatic drugs, *bDMARD* biological disease modifying antirheumatic drugs, *Pred* Prednis(ol)on.

Missing

[1] ESR: 3 (2 '0', 1 '≥1')
[2] CRP: 5 (4 '0', 1 '≥1')
[3] Anti-CCP: 121 (72 '0', 49 '≥1')
[4] Rf: 5 (5 '0', 0 '≥1')
[5] Erosions: 1 (0 '0', 1 '≥1')
[6] BMI: 12 (9 '0', 3 '≥1')
[7] DAS28: 41 (20 '0', 21 '≥1')
[8] Smoking status: 15 (10 '0', 5 '≥1')

Associations for clinically relevant differences in long-term outcome between groups

To examine the actual difference for the long-term outcome of the RAAD, between the usual care and T2T group, in combination with time to damage figure 5 illustrates the estimate time to assessed damaged joint (RAAD≥1). Because for some patients variables were missing, those were excluded from the analyses in this section and therefore from the 263 patients with RAAD-scores, 197 remain available for analysis. The estimate mean time in reaching damaged joints between the groups is 8.5 years in the usual care group and 7.6 years in the T2T group (95% CI usual care: 7.9 – 9.2, vs. T2T: 7.3 – 7.9). Based on the first survival analysis, table 8 reports no significant differences between the usual care and T2T group based on time to damage (HR1.65, 95% CI 0.98 – 2.76). Variables that were significant different between the groups and the outcome (RAAD=0 vs. (RAAD≥1), or variables that could be relevant as 'influencers', are used to examine whether they are associated to the long-term outcome of the RAAD-score.

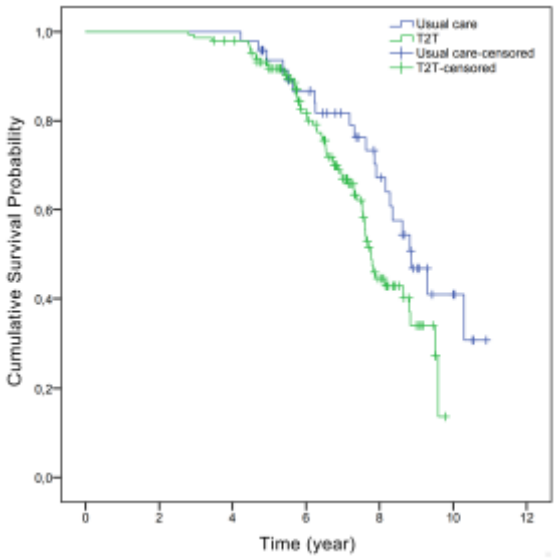

Figure 5 Kaplan-Meier overall survival of RA patients in the usual care and T2T group achieving ≥1 RAAD-score

In the univariate analyses the variables 'prednis(ol)one use before diagnosis' and 'first DAS28' are considered (cut-off point: $p<0.15$) significant different (both significant in table 3 and 7). Variables that are not significant different, but could be relevant to include in the multivariate analyses are: age, gender, time to first assessed RAAD-score and the mean DAS28 after 5 years. The relevance of these variables is based on a significant difference in one of the two tables (table 3 or table 7) or because of additional analysis that show significant differences such as the first assessed RAAD-score (appendix 2, figure 8). In appendix 3, the full detailed table with all p-values and Hazard ratios for each variable is presented.

Table 8 Cox regression multivariate analysis baseline variables

Variables (n=213)	**Multivariate, Hazard Ratio***	
	P	**95% C.I. for Exp (B)**
Group	0.056	1.65 (0.98 – 2.76)
Group, DAS28 (t=0), pred	0.242	1.38 (0.80 – 2.38)
Group, DAS28 (t=0), pred, age, sex	0.308	1.34 (0.76 – 2.34)
Group, DAS28 (t=0), pred, ESR, CRP, BMI	0.194	1.46 (0.82 – 2.59)
Group, DAS28 (t=0), pred, time to first RAAD	0.717	1.10 (0.65 – 1.88)
Group, DAS28 (t=0), pred, age, sex, time to first RAAD, DAS28 category, ESR, CRP, BMI, Erosion	0.870	1.05 (0.57 – 1.95)

DAS28 disease activity score in 28 joints, *Pred* Prednis(ol)on

*From Cox regression models with covariates.

(1) Reference

[1]Group: usual care

[2]Predni(sol)on previous: no

[3]Sex: male

[4]DAS28: remission

The first multivariate regression with only the significant variables (p<0.15: DAS28 and prednis(ol)on) reports no associations that significantly affect structural joint damage (Table 8). Multiple other multivariate analyses with other relevant variables report other findings. The combination of commonly used variables like age and sex, shows no associations. When we ad variables such as ESR, CRP and BMI, it seems ESR is associated to the outcome. A combination of the DAS28, predni(sol)on and time to first assessed RAAD-score reports significant findings of association between prednis(ol)on use before diagnosis (p<0.05) and the time to first RAAD-score (p<0.01), on the outcome. The last combination with all significant and relevant variables combined reports that age (p<0.05), erosion and time to first assessed RAAD-score (p<0.01) are significant related to the outcome and decrease the HR from 1.65 to 1.05. Meaning higher age increases the risk with 1.02, the presence of erosion with 2.89 an time until first RAAD-score with 0.28 (shorter time from diagnosis until RAAD-assessed results in earlier detection of damage).

Table 9 Distribution of outcomes relative to rheumatologists

	Rheumatologists					***P***
Variables	A	B	C	D	E	
Cohort, *n* (%)						<0.01
Usual care	57 (54.8%)	30 (47.6%)	45 (42.9%)	73 (59.8%)	45 (37.8%)	
T2T	47 (45.2%)	33 (52.4%)	60 (57.1%)	49 (40.2%)	74 (62.2%)	
RAAD, assessed, *n* (%)						<0.05
Yes	8 (7.7%)	8 (12.7%)	12 (11.4%)	49 (40.2%)	4 (3.4%)	
No	96 (92.3%)	55 (87.3%)	93 (88.6%)	73 (59.8%)	115 96.6%)	
DAS28, *n* (%)						<0.05
RDAS	33 (49.3%)	26 (56.5%)	48 (65.8%)	36 (46.2%)	60 (64.5%)	
LDAS	23 (34.3%)	9 (19.6%)	13 (17.8%)	18 (23.1%)	16 (17.2%)	
MDAS – HDAS	11 (16.4%)	11 (23.9%)	12 (16.4%)	24 (30.8%)	17 (18.3%)	
HAQ, mean ±SD	0.41 (±0.50)	0.53 (±0.62)	0.37 (±0.42)	0.43 (±0.42)	0.43 (±0.54)	
RAAD, *n* (%)						
0	22 (52.4%)	22 (53.7%)	30 (62.5%)	36 (58.1%)	38 (67.9%)	
1 – 4	17 (40.5%)	13 (31.7%)	16 (33.3%)	19 (30.6%)	17 (30.4%)	
≥5	3 (7.1%)	6 (14.6%)	2 (4.2%)	7 (11.3%)	1 (1.8%)	

RAAD Rheumatoid Arthritis Articular Damage score, *RAAD* Rheumatoid Arthritis Articular Damage score, moderate to high disease activity, *HAQ* Health Assessment Questionnaire, *DAS28* disease activity score in 28 joints: *RDAS* remission disease activity score, *LDAS* low disease activity score, *MDAS* moderate disease activity score, *HDAS* high disease .activity score

To evaluate further the differences between the rheumatologists table 9 reports the amount of patients treated per rheumatologist and the amount of patients assessed with RAAD-scores. The second objective of this study was to determine whether practice variation results in clinically relevant differences in short-term and long-term outcome. Because not all rheumatologists are included (due to certain conditions described in the method section) for these analyses 7 rheumatologists and 35 patients excluded, which means 5 rheumatologists with 513 patients were included. Table 9 shows the differences between the rheumatologists and in which group the patient is treated (p<0.01). The number of RAAD-scores assessed is reported as the number of patients for which the rheumatologists personally assessed the RAAD-score. Rheumatologists differ in their assessment of the RAAD-score, however we should also consider some cases the RAAD-score is assessed, but by a different rheumatologists. Which makes it look like some rheumatologists barely assess RAAD-scores by their patients, but their patients do contain RAAD-scores. The amount of patients in remission, with low, moderate or high disease activity, significantly differs between the rheumatologists (p<0.05). There are no significant differences based on the HAQ or RAAD-scores.

Discussion

This study provides further support for the use of T2T strategies in the treatment of early RA. The results of this study suggest that patient characteristics do not relate to the group (usual care or T2T) or treatment patients are assigned to. However, treatment strategy does influence the intermediate and long-term outcome after 5 to 10 years for RA. Compared to the usual care group patients in the T2T strategy (with RAAD-scores) achieve faster and more DAS28 remission during the entire first 5 years of treatment (50% vs. 64.3%), resulting in a better functional outcome (0.55 vs. 0.37), but not in significant differences of damaged joints (55.4% vs. 59.6%) after a follow-up of 5 – 10 years.

Compared to table 1 (n=548), the baseline characteristics of patients with a RAAD-score (n=263) in table 3 are similar, but also contain small differences. The first DAS28 are for both groups equal. In the usual care group, more patients died (23% vs. 15%), but also stopped the follow-up period because of remission (19% vs. 12%). Patients with RAAD-scores received more MTX, as well in the usual care (74.9% vs. 94.6%) as in the T2T group (99.3% vs. 100%) (p<0.01). Also the use of prednis(ol)on before RA diagnosis is slightly higher for the groups that contain RAAD-scores in table 3 (14.2% vs. 15.2%, and 4.6% vs. 4.1%). There is no difference in the use of biologicals in patients with RAAD-scores, compared to table 1 that does reports significant differences of biologicals (18% vs. 31%).

Besides more patients being in remission (51% vs. 59.3%), patients in the T2T group also achieve 8 months earlier remission (mean time 1.7 vs. 0. 9 years) compared to usual care. These results are also in line with findings of earlier studies that assess the relation between disease activity and T2T strategy (23–25). The mean HAQ is lower in the T2T group (0.55 vs. 0.37), which relates to the finding that patients treated with T2T usually have a HAQ score below 0.50 (11). The HAQ-scores improved between the first and second HAQ-score with 30% in the usual care group (0.63 vs. 0.44), and in the T2T group with 57% (0.44 vs. 0.19). Confirmed by sub analyzes, the HAQ is associated with DAS28 scores, in which patients with RDAS have better HAQ outcomes compared to patients with MDAS – HDAS with higher functional limitations. These relations are also find in other studies with strong associations (10–12,26,27).

There are no other studies that evaluate the RAAD-score in combination with T2T strategy. However the aim of the T2T strategy is to prevent long-term structural joint damage, which is evaluated in multiple studies by its influence on the long-term outcome in terms of HAQ and radiographic progression (28). Evaluating those results illustrates that tight control of the T2T results in low radiologic progression, especially in small joints but less in larger joints (29). Examining the long-term structural joint damage (RAAD) in this study, reports no large differences between the two groups. In the T2T group, a small portion of 4.2% patients contained less joint damage, (55% vs. 60%), however not significantly different compared to the usual care group. The findings of the sub analysis in table 6 underline the significant association between disease activity in the first years after onset if RA and outcome after 5 – 10 years: low disease activity corresponds to less joint damage. This confirms the relevance of the T2T aim of a DAS28 below 2.6, could therefore support the use of the novel RAAD-score as a tool, however does not reflect in the outcome of the groups with the RAAD-score. There are no significant differences between the usual care and T2T group of time until joint damage (HR1.65, 95% CI 0.98 – 2.76). Variables significant associated to the groups (usual care and T2T) and to the outcome of structural joint damage (RAAD=0, RAAD ≥1), or variables relevant for the multivariate decrease the HR from 1.65 to 1.05. The variables age, erosion at baseline and time until first assessed RAAD-score are significantly associated to structural joint damage.. Also the time until first RAAD-score affect the outcome: shorter time from diagnosis until RAAD-assessed results in earlier detection of damage. Since the RAAD is earlier assessed in patients treated with the T2T, this explains the difference in time until detection of joint damage between the groups.

The second objective of this study was to determine whether practice variation results in clinically relevant differences in intermediate and long-term outcome. Based on the results there are clinical differences between the rheumatologists based on the intermediate outcome of disease activity (DAS28) (p<0.05). Some rheumatologists do have more patients with lower disease activity compared to others. There is no unambiguous statement for this finding, but an explanation could be find in the findings of studies that examined guideline adherence. Guideline adherence relates to determinants of patient characteristics (DAS28) and rheumatologists characteristics (scientific education status) that influence why rheumatologists act in every patient's case. For example in cases of patients with DAS28>3.2, 67% of rheumatologists change the patients medication, others do not, which ultimately reflects in the DAS28 for their patients (15).

Besides the clinical differences there are also differences between the amount of patients treated in the T2T or usual care group (p<0.01). Reasons for this deviation could be related to guideline adherence, which is linked to 'lack of agreement', where some rheumatologist simply do not agree with the concept of a guideline, which reflects in the amount of patients treated in one of the two groups (16,30). Also patient-related barriers, such as patient preferences or patient background (comorbidity) resulting in rejecting of the treatment, could influence the group the patient in treated in (30). But we could also consider other determinants such as economic constraints or knowledge regarding the outcome of strategies, (16,31)

Because we have established that rheumatologist differ in allocating patients to one of the groups, there could be confounding by indication between the two groups. The reason for this distribution is unknown, but suggest some background influences from the patients (age, comorbidity) or rheumatologists (education) (32–34). Also the differences between the groups of patients lost to follow-up due to death suggest there is more going on. Another limitation related to the rheumatologists comes from including only rheumatologists for analysis who are comparable to each other. The reason for this comes from making the equitation 'fair' based on equal patients treated, however this excludes other cases with possible other results. The DAS28 scores are divided in categories by the mean DAS28 between the first 5 years. Which does not mean patients were consistently that DAS28 category over the entire study, the fluctuations of DAS28 over time are ignored, by presenting only the average DAS28 'dose'(10). For the RAAD analyses choices have been made to include hip joints. By this choice, the final RAAD-scores are for 11 patients higher and would have been distorted differently when the hip joint would have been excluded. Reasons for excluding the hip would have been because they may be related to osteoarthritis rather than RA. Missing values of baseline variables and comorbidity for the usual care group may lead to over- or underestimation of the treatment strategies outcomes (35). Also the limited number of HDAS patients makes it impossible to analyze how these patients are in relation to the long-term outcome measurements.

A major strength of this non-randomized controlled study are the results from daily clinical practice. It tells us what actually happens over a longer period of time, and what that entails for short- and long-term outcomes. Also, compared to other studies, this study with a good sample size of patients (n=548) gives a good representation of the intervention effects (2). At last, the evaluation for RAAD and HAQ scores after 5 to 10 years in relation to treatment strategies, contributes to our knowledge of the long-term outcomes for RA patients.

It is recommended for future research to analyze the complex relation between structural joint damage and the presence of other background determinants (e.g. comorbidity, rheumatologists education) that could influence the outcome of structural joint damage within a randomized controlled setting of the T2T strategy, with a higher RAAD-score rate in both groups.

Conclusion

T2T strategy is superior to usual care in achieving faster remission and better disease activity. Patients who are in remission are more likely to have better long-term outcome. Structural joint damage is not significantly more present in the usual care or T2T group, yet more patients in the T2T group do have better functional ability. Structural joint damage is associated with baseline variables age and erosion. Rheumatologists have a preference and therefore influence in which group the patient is treated, with clinical differences of the DAS28 scores.

Competing interest

None declared.

Ethics approval

The medical ethics committees of the Medisch Spectrum Twente, Enschede exempt this study from ethical approval, in accordance with Dutch law of Medical Research Involving Human Subjects Act, because the T2T patients have been informed in the past concerning their treatment data being used for research and no action or behavior is imposed on participating patients.

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Appendix

Appendix 1: Informed consent form

[Composed by the ZGT in 2006]

Patiënt informatie behandeling nieuw gediagnosticeerde reumatoïde artritis.

Bij u is reumatoïde artritis vastgesteld. In deze informatiebrief wordt u uitgelegd hoe uw behandeling er uit zal zien.

De behandeling:

Wetenschappelijk onderzoek laat zien dat het snel tot rust brengen van gewrichtsontstekingen bij patiënten met reumatoïde artritis steeds beter lukt. Doel van onze behandeling is om bij mensen bij wie onlangs de diagnose reumatoïde artritis gesteld is de reumatoïde artritis zo snel mogelijk helemaal tot rust te brengen (in remissie). Een belangrijke rol hierbij spelen zogenoemde TNF-blokkerende medicijnen. Deze medicijnen blokkeren het ontstekingseiwit TNF dat een belangrijke rol speelt bij gewrichtsontstekingen op basis van reumatoïde artritis. Hierdoor neemt de ontsteking in de gewrichten af met daardoor minder pijn en gewrichtsbeschadiging. In Nederland kunnen deze medicijnen echter pas voorgeschreven worden als tenminste twee andere reumamedicijnen voldoende zijn uitgeprobeerd. We willen bereiken dat we bij u de reumatoïde artritis zo snel mogelijk tot rust kunnen brengen in een zo vroeg mogelijk stadium van de ziekte door middel van optimaal gebruik van de momenteel beschikbare medicamenten en door, als het nodig is, ook zo snel mogelijk te starten met deze TNF-blokkerende medicijnen. U zult daarom behandeld worden volgens een vast behandelschema van medicamenten met tevoren vastgestelde beslismomenten over het aanpassen van de medicatie (zie tabel). Als de reuma niet rustig is, wordt de volgende stap in het schema gezet. Als de reuma wel rustig is blijft u doorgaan met de medicijnen die u op dat moment gebruikt. Omdat er aanwijzingen zijn dat bij blijvende remissie (geen gewrichtsontstekingen) deze medicijnen na verloop van tijd ook weer gestaakt kunnen worden zonder dat dit leidt tot het opnieuw optreden van gewrichtsontstekingen willen we bij patiënten bij wie de reumatoïde artritis langere tijd helemaal rustig is proberen de medicijnen weer af te bouwen en uiteindelijk proberen te stoppen.

Medicatieschema:

Week 0	MTX 15mg/week
Week 8	MTX 25mg/week
Week 12	MTX 25mg/week en SSZ 2dd1000mg
Week 20	MTX 25mg/week en SSZ 3dd1000mg
Week 24	MTX 25mg/week en adalimumab 40mg/2wk
Week 36	MTX 25mg/week en adalimumab 40mg/wk
Week 48-52	MTX 25mg/week en etanercept 50mg/wk
1 jaar en 3 maanden	MTX 25mg/week en infliximab 3mg/kg/8wk
1 jaar en 6 maanden	MTX 25mg/week en infliximab 3mg/kg/4wk

MTX=methotrexaat, SSZ=sulfasalazine.

Alle patiënten met kort bestaande reumatoïde artritis die ouder dan 18 jaar zijn kunnen op deze manier behandeld worden. Bij patiënten met zwangerschapswens of die zwanger zijn wordt een aangepast medicatieschema gevolgd.

De afspraken op de polikliniek:

Elke 2-3 maanden bezoeken de patiënten de polikliniek reumatologie voor een visite bij een reumaverpleegkundige. In het begin van de behandeling kan dit wat vaker zijn. Daarnaast wordt de patiënt tenminste een keer per jaar gezien door de reumatoloog. Tijdens elke visite zal er een gewrichtsonderzoek worden gedaan en zult u gevraagd worden enkele vragenlijsten betreffende uw dagelijks functioneren en algemene gezondheidstoestand in te vullen. In verband met het gebruik van medicatie voor de reumatoïde artritis en om inzicht te krijgen in de mate van ziekteactiviteit zal laboratoriumonderzoek noodzakelijk zijn. Tevens zullen met enige regelmaat röntgenfoto's van handen en voeten gemaakt worden.

Gebruik gegevens:

De verzamelde gegevens over uw ziekte willen we graag gebruiken voor wetenschappelijk onderzoek. We vragen uw toestemming hiervoor via bijgevoegd formulier. U bent te allen tijde vrij uw toestemming weer in te trekken. Het niet verlenen van toestemming heeft geen consequenties voor uw behandeling.

Hebt u na het lezen van deze brief nog vragen, bespreek deze dan met uw reumatoloog of verpleegkundige tijdens uw volgende afspraak of neem contact op via het secretariaat reumatologie: tel. 0546693404.

TOESTEMMINGSFORMULIER:

Hierbij verklaart ondergetekende dhr./mevr. ……, geboren ……, dat de gegevens die worden verzameld in het kader van zijn/haar behandeling voor reumatoïde artritis mogen worden gebruikt voor wetenschappelijk onderzoek.

Handtekening patiënt (e): ……..

Datum: ……..

Hierbij verklaart de behandelend reumatoloog ……., dat hij/zij dhr./mevr.…… heeft uitgelegd dat de verzamelde gegevens worden gebruikt voor wetenschappelijk onderzoek. Met de gegevens zal vertrouwelijk worden omgegaan.

Handtekening reumatoloog: …….

Datum: …….

Appendix 2: Survival analysis

Survival time per group: end follow-up

From the total target group (*n*=548), for 505 (237 usual care, 268 T2T) patients, their end-date was available to analyze the total follow-up time from diagnosis to end follow-up (reasons: deceased, remission, other). Figure 6 illustrates the difference in the overall follow-up time (Long Rank (Mantel-Cox): $p<0.01$): patients in the usual care group have a mean follow-up of 7.6 years, in the T2T group 8.9 years (95% confidence interval [CI] usual care: 7.1 – 8.1, vs. T2T: 8.5 – 9.3).

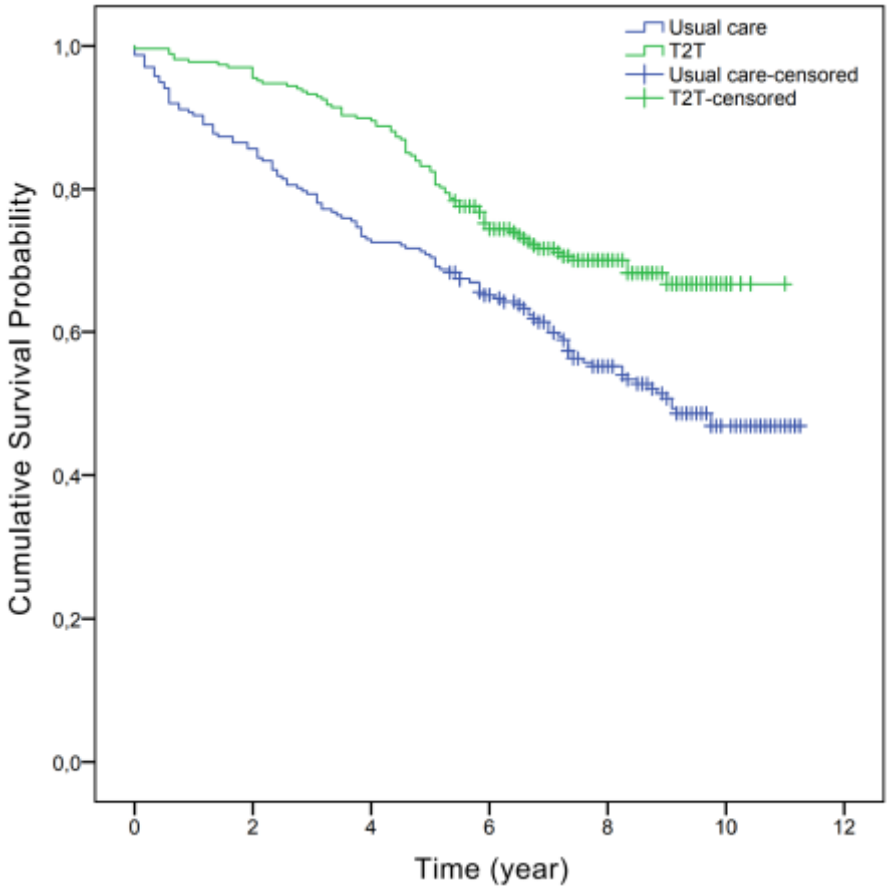

Figure 6 Kaplan-Meier follow-up time diagnosis until end follow-up in years.

Survival time per group: time until first assessed HAQ-score

From the total target group (*n*=548), 204 (69 usual care, 135 T2T) patients contained HAQ-scores. Figure 7 illustrates there is a difference in the overall time until first assessed HAQ-score. (Long Rank (Mantel-Cox): $p<0.01$): patients in the usual care group have a mean time to first HAQ-score assessed of 7.3 years, in the T2T group 6.7 years (95% confidence interval [CI] usual care: 6.8 – 7.7, vs. T2T: 6.5 – 6.9).

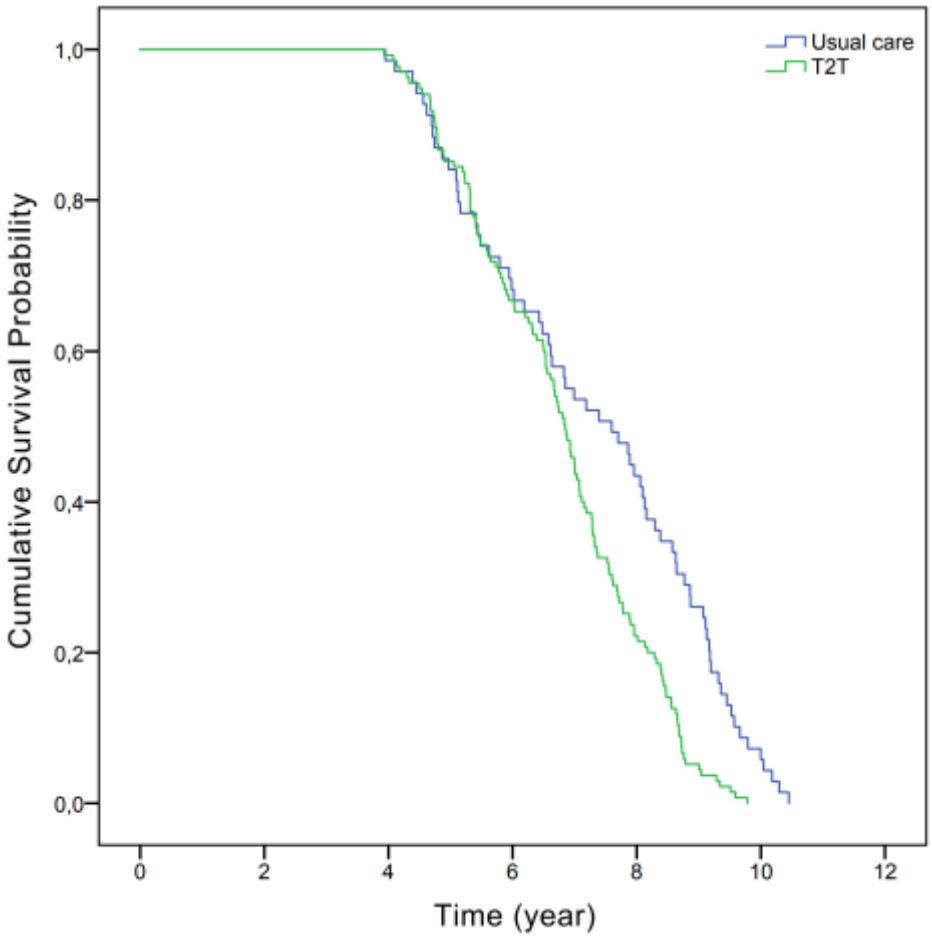

Figure 7 Kaplan-Meier time until first assessed HAQ-score in years.

Survival time per group: time until first assessed RAAD-score

From the total target group (*n*=548), 263 (92 usual care, 171 T2T) patients contained HAQ-scores. Figure 7 illustrates there is a difference in the overall time until first assessed RAAD-score. (Long Rank (Mantel-Cox): $p<0.01$): patients in the usual care group have a mean time to first HAQ-score assessed of 7.2 years, in the T2T group 6.3 years (95% confidence interval [CI] usual care: 6.9 – 7.7, vs. T2T: 6.1 – 6.6).

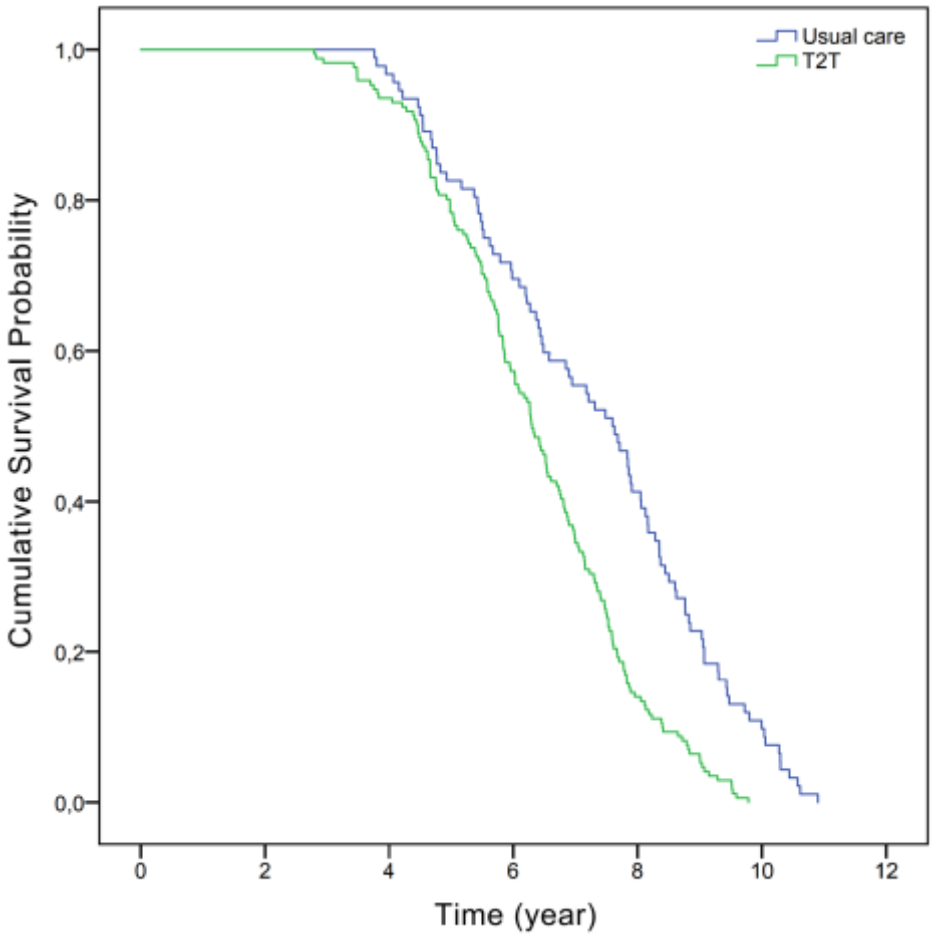

Figure 8 Kaplan-Meier time until first assessed RAAD-score in years.

Appendix 3: Detailed multivariate regression output

Table 10 Cox regression multivariate analysis baseline variables

Variables (n=213)	**Multivariate, Hazard Ratio***	
	P	**95% C.I. for Exp (B)**
Group	0.056	1.65 (0.98 – 2.76)
Group, DAS28 (t=0), pred	0.242	1.38 (0.80 – 2.38)
DAS28 (t=0)	0.097	1.14 (0.97 – 1.34)
Pred	0.107	1.91 (0.87 – 4.18)
Group, DAS28 (t=0), pred, age, sex	0.308	1.34 (0.76 – 2.34)
DAS28 (t=0)	0.137	1.13 (0.96 – 1.32)
Pred	0.123	1.85 (0.84 – 4.09)
Age	0.154	1.01 (0.99 – 1.03)
Sex	0.407	1.21 (0.76 – 1.92)
Group, DAS28 (t=0), pred, ESR, CRP, BMI	0.194	1.46 (0.82 – 2.59)
DAS28	0.243	1.10 (0.93 – 1.31)
Pred	0.108	1.94 (0.86 – 4.35)
ESR	0.044	1.01 (1.00 – 1.03)
CRP	0.395	0.99 (0.98 – 1.00)
BMI	0.975	1.00 (0.95 – 1.05)
Group, pred, DAS28 (t=0), time to first RAAD	0.717	1.10 (0.65 – 1.88)
DAS28 (t=0)	0.053	1.17 (0.99 – 1.36)
Pred	0.016	2.76 (1.21 – 6.31)
Time to first RAAD	0.000	0.34 (0.28 – 0.43)
Group, pred, DAS28 (t=0), age, sex, time to first RAAD, DAS28 category, ESR, CRP, BMI, Erosion	0.870	1.05 (0.57 – 1.95)
DAS28 (t=0)	0.408	1.08 (0.90 – 1.30)
Pred	0.145	1.92 (0.80 – 4.64)
Age	0.017	1.02 (1.00 – 1.04)
Sex	0.652	1.12 (0.68 – 1.86)
ESR	0.239	1.01 (0.99 – 1.02)
CRP	0.393	1.00 (0.99 – 1.01)
BMI	0.292	1.03 (0.97 – 1.09)
Erosion	0.000	2.89 (1.66 – 5.03)
Time to first RAAD	0.000	0.28 (0.22 – 0.36)
DAS28 category		
RDAS	1	1
LDAS	0.283	1.37 (0.77 – 2.44)
MDAS – HDAS	0.335	1.34 (0.74 – 2.42)

DAS28 disease activity score in 28 joints: *RDAS* remission disease activity score, *LDAS* low disease activity score, *MDAS* moderate disease activity score, *HDAS* high disease activity score, *Pred* Prednis(ol)on

*From Cox regression models with covariates. Underlined = significant different (p<0.05)

(1) Reference

[1]Group: usual care

[2]Predni(sol)on previous: no

[3]Sex: male

[4]DAS28: remission

Appendix 4: Ethical approval METC & ALU

UNIVERSITY OF TWENTE.