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ORIGINAL RESEARCH

What is the best target in a treat-to-target strategy in rheumatoid arthritis? Results from a systematic review and meta-regression analysis

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ABSTRACT

Objectives A treat-to-target (T2T) strategy has been shown to be superior to usual care in rheumatoid arthritis (RA), but the optimal target remains unknown. Targets are based on a disease activity measure (eg, Disease Activity Score-28 (DAS28), Simplified Disease Activity Indices/Clinical Disease Activity Indices (SDAI/CDAI), and a cut-off such as remission or low disease activity (LDA)). Our aim was to compare the effect of different targets on clinical and radiographic outcomes.

Methods Cochrane, Embase and (pre)MEDLINE databases were searched (1 June 2022) for randomised controlled trials and cohort studies after 2003 that applied T2T in RA patients for ≥12 months. Data were extracted from individual T2T study arms; risk of bias was assessed with the Cochrane Collaboration tool. Using meta-regression, we evaluated the effect of the target used on clinical and radiographic outcomes, correcting for heterogeneity between and within studies.

Results 115 treatment arms were used in the meta-regression analyses. Aiming for SDAI/CDAI-LDA was statistically superior to targeting DAS-LDA regarding DAS-remission and SDAI/CDAI/Boolean-remission outcomes over 1–3 years. Aiming for SDAI/CDAI-LDA was also significantly superior to DAS-remission regarding both SDAI/CDAI/Boolean-remission (over 1–3 years) and mean SDAI/CDAI (over 1 year). Targeting DAS-remission rather than DAS-LDA only improved the percentage of patients in DAS-remission, and only statistically significantly after 2–3 years of T2T. No differences were observed in Health Assessment Questionnaire and radiographic progression.

Conclusions Targeting SDAI/CDAI-LDA, and to a lesser extent DAS-remission, may be superior to targeting DAS-LDA regarding several clinical outcomes. However, due to the risk of residual confounding and the lack of data on (over)treatment and safety, future studies should aim to directly and comprehensively compare targets.

PROSPERO registration number CRD42021249015.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although a treat-to-target-strategy has been shown to be superior to usual care in rheumatoid arthritis (RA), there is a lack of evidence and consensus about the optimal treatment target. Consequently, different targets are used in clinical practice and recommended in international guidelines.

WHAT THIS STUDY ADDS

⇒ Results of our indirect comparison using meta-regression analysis show that the target of Simplified Disease Activity Indices/Clinical Disease Activity Indices-low disease activity (LDA), and to a lesser extent Disease Activity Score (DAS)-remission, performed better than DAS-LDA regarding disease activity, but not functioning or radiographic progression. Insufficient data were available to analyse safety or medication use.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results of this study may inform future studies comparing treatment targets head to head, and may subsequently further improve RA care.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterised by inflammation of synovial joints, although other organ systems can also be involved.[1] Treatment is aimed at limiting and controlling disease activity, as prolonged high levels of activity increase the risk of progressive joint damage and mortality.[2–4] In the proactive treat-to-target (T2T) strategy, disease activity is frequently and systematically assessed using a validated measure, which is then compared with a prespecified treatment target. If the target is not reached within a particular time frame, treatment is intensified accordingly.[5]

Targets are commonly based on a composite Disease Activity Score with a cut-off value for remission or low disease activity (LDA).[6]

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Examples of composite scores include the DAS (counting 28 or 44 joints in the DAS28/DAS44 respectively), the Simplified and the Clinical Disease Activity Indices (SDAI/CDAI).[7] The DAS variants are based on tender and swollen joint counts (TJC/SJC), the erythrocyte sedimentation rate (ESR) or C reactive protein (CRP), and the patient's global assessment of disease activity (PGA) on a Visual Analogue Scale (VAS).[8] Although the DAS is well established and validated, it has been criticised for allowing a high SJC while fulfilling the definition of remission, due to calculation effects.[9] The SDAI and CDAI weigh the individual components equally and have added the physicians assessment of disease activity. The CDAI does not include any laboratory marker, making it easier to apply in clinical practice, but also less objective.

Alternative to the composite scores, a target may also be defined using a Boolean definition, for example, American College of Rheumatology / European Alliance of Associations of Rheumatology (ACR/EULAR) remission. Here, a set of core variables (TJC/SJC, PGA and CRP) must all have a value of ≤1. As the original Boolean criteria were criticised for being too stringent, the recently revised criteria have loosened the maximal PGA to 2 cm on a 10 cm VAS.[10]

While T2T has been shown to be superior to the (previous) standard of usual care, the direct comparison of different treatment targets is insufficiently studied.[5 11–13] Therefore, it remains unknown what the optimal target in a T2T strategy is, and thus different targets are used in clinical practice and recommended in international guidelines.[5 13 14] Specifying the optimal treatment target is important: too lenient a target may result in undertreatment and a higher disease burden. Conversely, too stringent a target may lead to overtreatment, side effects, patient dissatisfaction and unnecessary costs. Both situations may negatively impact patients' quality of life. Accordingly, determining the optimal treatment target has been included in the research agenda of the 2022 EULAR recommendations.[13]

As the T2T strategy has been generally accepted and recommended for some time, many recent clinical studies evaluating a specific drug or treatment strategy as primary objective apply a T2T approach.[5 15] In the current study, we exploited this available evidence by performing a systematic literature review and meta-regression analysis. Our aim was to compare the effect of different treatment targets on clinical and radiographic outcomes in patients with RA.

METHODS
Protocol and registration
Prior to commencing this study, the protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO, number: CRD42021249015). This systematic review was performed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16]

Literature search
The databases (pre)MEDLINE, Cochrane and Embase were searched, combining synonyms and MeSH terms for T2T and RA. Studies published in English (due to lack of fluency in other languages) after 2003 were included, as after this date the use of biological disease-modifying antirheumatic drugs (bDMARDs) and the T2T-principle became common in clinical studies. In addition to original research papers, reviews were included for reference screening of other relevant articles. For a full overview of the search strategy as performed on 1 June 2022, see online supplemental figures S1–S4.

Study selection
Identified articles were deduplicated and uploaded to a reference management programme (Rayyan), where MAM and FEM independently performed title, abstract and subsequent full-text screening. Randomised controlled trials (RCTs) and cohort studies were included if they applied a T2T-strategy in RA patients for ≥12 months. T2T was defined as the frequent (≤4 monthly) assessment of disease activity using a validated measure (ie, DAS28/44-ESR/CRP, SDAI, CDAI, RADAI, RAPID3, Boolean remission or a SJC), which is compared with a prespecified treatment target. If the target is not met, DMARD-treatment should be intensified. Studies with a sample size of ≥50 patients and ≥1 T2T-treatment arm could be included. Outcomes of interest were disease activity, radiographic progression, functional status, bDMARD use and safety after ≥12 months of T2T. These measures could be expressed continuously or as a response percentage. Disagreements were discussed among FEM, MAM, PMJW and AAdB until consensus was reached.

Data extraction
Data extraction was performed independently by MAM and EM using a predefined form; discrepancies were double-checked with the source data. Data extraction was performed per treatment arm that applied a T2T strategy (eg, if an RCT reported 2-year results for 3 T2T-treatment arms, these were extracted separately). Only time points when T2T treatment was continued were considered. When outcomes were present at multiple time points (eg, 1 and 2 years) these were extracted as separate arms. See table 1 for an overview of the extracted data.

Risk of bias assessment
Risk of bias (RoB) assessment was performed independently by FEM and MAM using the Cochrane Collaboration tool.[17] All domains were assessed, except the randomisation domain for cohort studies as this is not applicable to this design. Disagreements were discussed among FEM, MAM, PMJW and AAdB until consensus was reached.

Table 1 Overview of extracted data from included articles

Study characteristics	Baseline characteristics	Outcome measures*
Title	Mean/median	
Publication year	SDAI, CDAI or DAS and their components	(Change in) SDAI, CDAI or DAS and their components
Study type (RCT or cohort)	SF-survey	SF-survey
Treatment target	Fatigue and pain on a VAS	Fatigue and pain on a VAS
Drug treatment protocol	HAQ-score	HAQ score
Interval between assessments	SHS-score and components	SHS-score and components
No of patients	Age and symptom duration	
	Proportion of patients	
	Female	Remission (drug-free, Boolean, DAS, SDAI or CDAI) and LDA
	Early† vs established RA	Relevant radiographic progression
	Erosions	Erosions
	RF/ACPA positive patients	AE/SAE
		Use of bDMARDs

*Regarding outcome measures, the time point, the outcome value and the measure of spread (ie, SD, CI or IQR) were extracted.
†Early RA was based on the definition given in the articles, which was usually either <1 year or <2 years disease duration.
ACPA, anticitrullinated protein antibody; AE, adverse events; bDMARD, biological disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; LDA, low disease activity; RA, rheumatoid arthritis; RCT, randomised controlled trial; RF, rheumatoid factor; SAE, serious adverse event; SDAI, Simplified Disease Activity Index; SF, Short Form Health Survey; SHS, Sharp van der Heijde score; VAS, Visual Analogue Scale.

Data preprocessing for meta-regression analysis

To prepare the data for meta-regression analysis, we selected arms that reported the same outcome measure (eg, DAS-remission) at the same time point (ie, '1', '2–3', '4–6' or '>6' years) for each analysis. A minimum of 10 arms was deemed required for a relevant analysis. Treatment targets that were used in ≤2 studies were excluded from analysis, which was the case for Boolean-remission and SDAI-remission and an SJC of 0. The targets SDAI-LDA and CDAI-LDA were grouped together, as these were uncommon and were deemed sufficiently similar.[18] Similarly, for the targets of DAS-remission and DAS-LDA, the different DAS-variants were combined (ie, DAS28/44 using ESR or CRP). Regarding

outcome measures, SDAI-remission, CDAI-remission and Boolean remission were grouped together, for which we corrected in the meta-regression analysis (see below). Of note, the trials included in this study did not yet incorporate the revised 2022 ACR/EULAR Boolean criteria.[10] To standardise scales of different DAS variants, mean DAS44-ESR and DAS28-CRP measures were converted to DAS28-ESR according to published translation formulae, as DAS28-ESR was most commonly reported (27 of 52 mean DAS analyses).[19 20] For the SHS outcome, the mean change per year was calculated in order to correct for limited differences in the duration of follow-up, as the SHS is a cumulative measure and can typically only increase over time.

Changes from baseline in disease activity/Health Assessment Questionnaire (HAQ)/SHS were transformed to outcome values at endpoint when needed using the baseline value. The SD of the score at endpoint was calculated using a correlation coefficient, in accordance with the Cochrane handbook for systematic reviews (needed for 78 of 165 arms).[21] For the HAQ, a correlation coefficient of 0.6 was assumed to determine the SD of the outcome due to insufficient data for 17 of 58 arms. When only medians and IQRs were reported (28 of 165 mean outcome analyses), means and SDs were estimated based on the formulas provided by Wan et al.[22]

Meta-regression analysis

Meta-regression analyses were performed with the R package 'metafor' (rma.mv function) for multilevel meta-analytic regression models. Both 'study' and 'arm' were added as random effects in all analyses, where 'study' refers to an overarching clinical trial (eg, BeST or OPERA) and 'arm' refers to the individual treatment arms. This was done to account for the heterogeneity between and within studies, as often multiple arms from one study were included. In the metaregression analyses, each arm is attributed a weight based on the SE, thus correcting for small sample sizes.

We first estimated the effect of the treatment target on the outcome at a certain timepoint in a univariate model. Subsequently, a full (adjusted) model was composed, adding the following covariates: early or established RA, the availability of bDMARDs, the baseline value of the outcome variable, and whether the treatment intensifications were formalised in a protocol. For remission outcomes, we corrected for the baseline DAS and the specific type of remission (eg, DAS44-ESR or SDAI based), for which we also performed subgroup analyses. For yearly SHS progression, a non-linear association for baseline SHS was also explored using a squared term, given its importance and the known ceiling effect of the SHS.[23] The selection of covariates was based on clinical expertise, variables' availability and impact on the outcome in bivariate analyses from the extracted variables (see the Data extraction section). The primary variables of interest for the full model (ie, target, outcome, covariates: early/established RA, availability of bDMARDs,

baseline value outcome variable and presence of a formal treatment protocol) were available for all arms included in this study.

If there was no need to correct for one or two of the selected covariates due to a lack of variation (eg, if all treatment arms were early RA), the mean percentage RF and/or ACPA-positive patients and symptom duration were explored as covariates. This was the case for three analyses: SHS progression at year 1, mean DAS28-ESR at 2–3 years and DAS remission at 4–6 years.

From the full model, a parsimonious model was derived in which covariates with little effect were removed from the model. Covariates with a $p > 0.2$ were removed, starting with the covariate with the highest p value. If this removal resulted in a change of (any of) the regression coefficient(s) for the treatment target(s) of ≥15% with a minimum absolute effect of 0.05/0.005 for means/proportions respectively, the covariate was kept in the model. If these criteria were not met, the covariate was removed. Subsequently, the next covariate with the highest $p > 0.2$ was removed and evaluated in the same way. This process was iterated until no more variables could be removed, resulting in the parsimonious model. The baseline value of the outcome variable was always retained.

Although normal distributions of the outcome variables are to be expected based on the central limit theorem, a natural log transformation was performed if the residuals of the parsimonious model had a skewness exceeding −2/+2 or kurtosis exceeding −7/+7, in addition to an untransformed sensitivity analysis.[24–26] Subgroup analyses were performed for early vs established RA, remission types and RCT versus cohort studies, if ≥5 arms per subgroup were available. Additionally, we performed sensitivity analyses, using the parsimonious models, by excluding high RoB papers and by performing 'leave-one-out' analyses. In the latter, the same analysis is performed numerous times, excluding one arm in each analysis, in order to assess the influence of individual arms. The minimum and maximum effects of the 'leave-one-out' analyses are reported.

RESULTS

Study selection and characteristics

Of the 3879 articles identified through the literature search, 66 articles were selected after title, abstract, full-text and reference screening (figure 1).[27–92] Characteristics of selected articles including RoB assessments are shown in online supplemental table S1. These 66 selected articles concerned results from 40 studies, and from these the data of 169 treatment arms were extracted. Of the 66 articles/169 arms extracted, the data of 52 articles/114 arms were used in the meta-regression analyses. Reasons not to use treatment arms in the analysis are stated in online supplemental table S1 and include: reported outcome measure was present in an insufficient number of arms (<10, eg, bDMARD use and adverse events
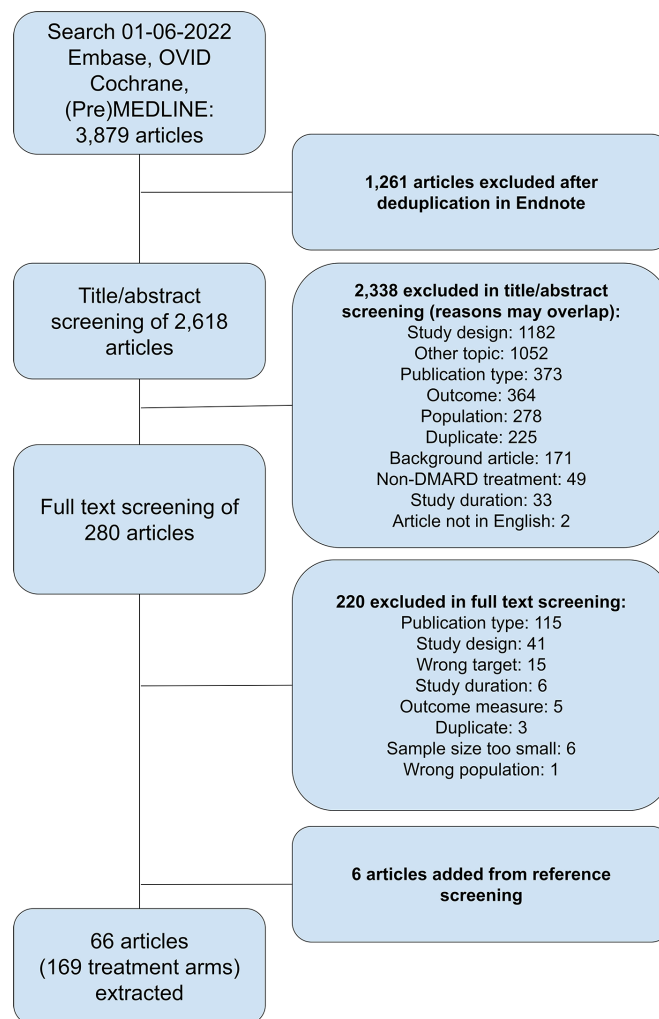

Figure 1 Flow chart of article selection. DMARD, disease-modifying antirheumatic drug.

(AEs)), insufficient arms at a particular time point (eg, after >6 years of T2T), or duplicate results with another arm (eg, 2 arms that both report mean DAS after 1 year in the BeSt-trial). The characteristics of the 114 treatment arms used in the meta-regression analyses are shown in table 2.

Meta-regression analyses

For a full overview of the target regression coefficients and confidence intervals of the parsimonious, full and univariate models, see online supplemental tables S2–S10.

Outcome mean DAS28-ESR

Targeting either SDAI/CDAI-LDA or DAS-remission rather than DAS-LDA gave a non-statistically significant improvement of the mean DAS28-ESR after 1–3 years of T2T, see figure 2A. There were no differences between the target of SDAI/CDAI-LDA and DAS-remission (online supplemental tables S2 and S3).

Outcome percentage DAS-remission

Aiming for SDAI/CDAI-LDA rather than DAS-LDA significantly improved the percentage of patients in

Table 2 Characteristics of treatment arms used in the meta-regression analyses

Arms used in analyses, n	114
Arms with T2T target DAS28/44-LDA, n (%)	71 (62.3)
Arms with T2T target DAS28/44-remission, n (%)	36 (31.6)
Arms with T2T target SDAI-CDAI LDA, n (%)	7 (6.1)
Publication year	
2003–2009, n(%)	13 (11.4)
2010–2015, n(%)	35 (30.7)
2016–2022, n(%)	66 (57.9)
% Female, mean (SD) (115 arms)	70.0 (6.7)
Age, mean (SD) (103 arms)	54.3 (4.6)
%RF positive, mean (SD) (107 arms)	64.7 (15.9)
%ACPA positive, mean (SD) (94 arms)	66.5 (16.2)
Baseline DAS, mean (SD) (109 arms)	5.0 (0.8)
Baseline HAQ, mean (SD) (66 arms)	1.2 (0.3)
Baseline SHS, median (IQR) (57 arms)	3.0 (1.3–7.0)
Early RA*, n (%) (115 arms)	100 (87.7)
bDMARD available, n (%) (115 arms)	80 (70.2)
Formal treatment protocol, n (%) (115 arms)	89 (78.1)
Outcome DAS28/44 remission, mean % (SD) (88 arms)	55.9 (16.8)
Outcome SDAI/CDAI/Boolean remission, mean % (SD) (67 arms)	37.2 (14.5)
Outcome DAS28-ESR, mean (SD) (51 arms)	2.8 (0.6)
Outcome SDAI/CDAI, median (IQR) (16 arms)	4.5 (2.6–5.6)
Outcome HAQ, mean (SD) (66 arms)	0.6 (0.2)
Outcome SHS, median (IQR) (57 arms)	6.0 (1.9–12.4)

*Early RA was based on the definition given in the articles, which was usually either <1 year or <2 years disease duration.
ACPA, anticitrullinated protein antibodies; bDMARD, biological disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; DAS, Disease Activity Score; HAQ, Health Assessment Questionnaire; LDA, low disease activity; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; SHS, Sharp van der Heijde Score; T2T, treat to target.

DAS-remission after 1–3 years of T2T, see figure 2B. There were no differences between the SDAI/CDAI-LDA and DAS-remission targets (online supplemental tables S2 and S3). Compared with DAS-LDA, the target of DAS-remission significantly improved the percentage of patients in DAS-remission at 2–3 years with 21% (percentage points, eg, from 50% to 71%, p=0.03). At year 1, only a trend was observed (p=0.11), with only a statistically significant effect on the outcome DAS44-ESR-remission (38%, p<0.0001). After 4–6 years, no

significant improvement was observed when targeting DAS-remission versus DAS-LDA (10%, p=0.53, online supplemental table S4).

Outcome mean SDAI/CDAI
After 1 year of T2T, targeting SDAI/CDAI-LDA compared with DAS-remission significantly improved the mean SDAI/CDAI with 5.08 units (p=0.03), see online supplemental table S2). Compared with to DAS-LDA, only a non-statisically significant mean improvement of 2.03 units (p=0.23) was observed (figure 2C). Targeting DAS-remission compared with DAS-LDA, gave a non-statistically significant deterioration of mean SDAI/CDAI of −3.05 (p=0.06).

Outcome percentage SDAI/CDAI/Boolean remission
Targeting SDAI/CDAI-LDA significantly improved the percentage of patients in SDAI/CDAI/Boolean remission compared with both DAS-LDA and DAS-remission targets, after 1 year (borderline significant for DAS-LDA) and 2–3 years (year 1: 34% p=0.05 and 35% p=0.03 for comparison to DAS-LDA and DAS-remission respectively, year 2–3: 31% p=0.0002 and 36% p<0.0001) (see figure 2D and online supplemental tables S2 and S3). There were no clear differences between the targets of DAS-remission and DAS-LDA, nor did the subgroup analysis of the remission outcome types (SDAI/CDAI vs Boolean remission) differ substantially from the overall analysis.

Outcome yearly progression of SHS
No differences between targeting DAS-remission and DAS-LDA were found for yearly SHS progression, although surprisingly, a numerical deterioration was found for targeting DAS-remission versus DAS-LDA, after both 1 year of T2T (−0.09, p=0.66) and 2–3 years of T2T (−0.20, p=0.26). See figure 2E. A similar trend was present in the untransformed sensitivity analyses at years 1 and 2 (−0.19, p=0.75 and −0.40, p=0.21 respectively). For the analysis of SHS progression at year 1, one arm that did not report the mean percentage RF nor ACPA-positive patients was removed from the primary analysis, in order to add this covariate to the model. As a sensitivity analysis, we added this arm to the model, and left out the RF/ACPA variable, which did not greatly affect results (−0.09 p=0.66 to −0.15 p=0.44).

Outcome mean HAQ
We observed no differences between targets at years 1–3 for the mean HAQ (see figure 2F).

Outcome mean CRP
Given the subjective nature of many of the outcome measures, we also analysed the more objective outcome of CRP. The target of SDAI/CDAI-LDA but not the target of DAS-remission non-significantly reduced mean CRP at year 1 (−2.01, p=0.54 and −0.01, p=0.99) compared with the DAS-LDA target.
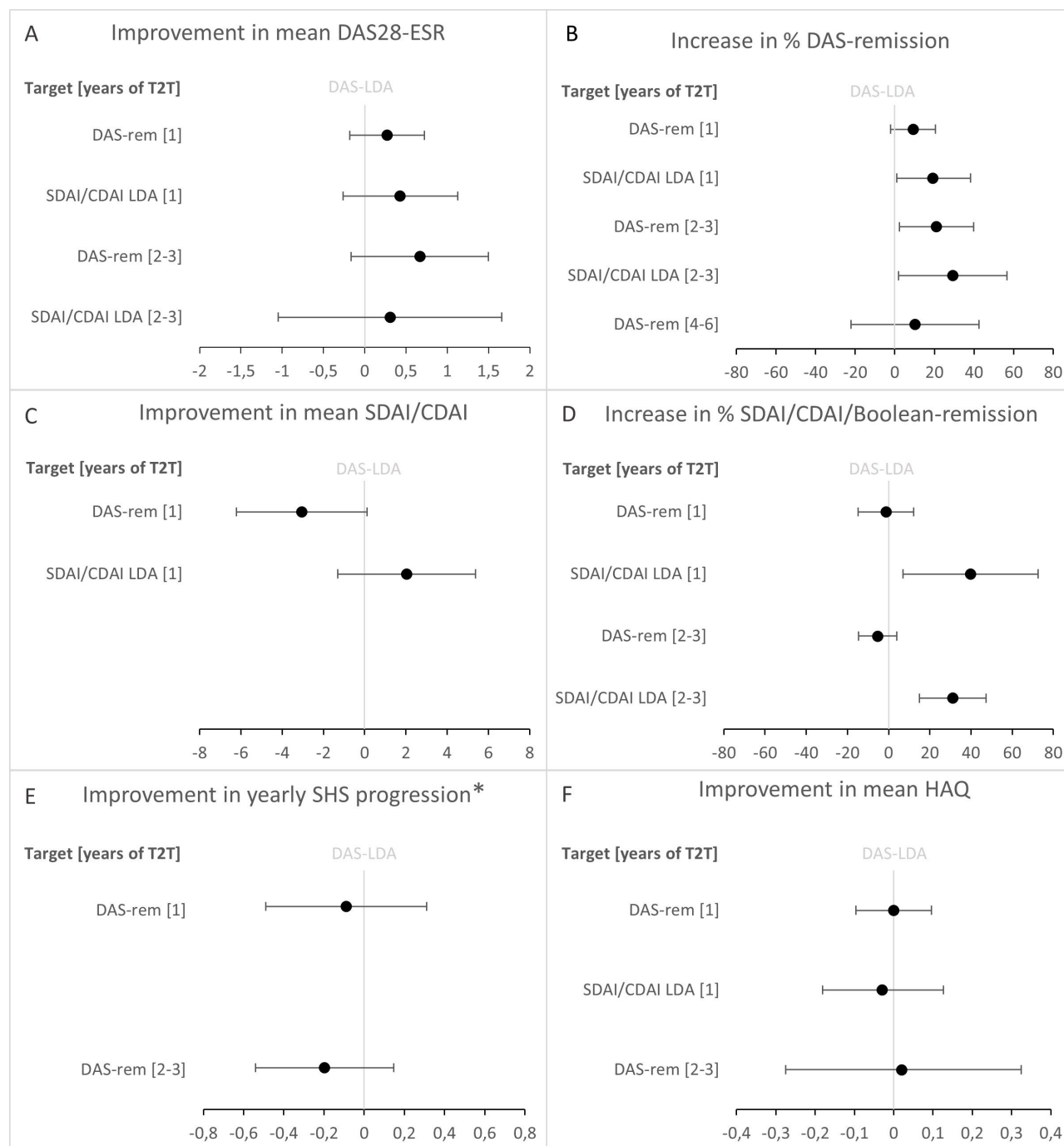
Figure 2 Effect of the DAS28/44-remission and SDAI/CDAI-LDA treatment targets compared with the target of DAS28/44-LDA, on different outcomes and at different time points based on meta-regression analyses (parsimonious models). Results are presented in comparison to a treatment target of DAS-LDA. Exact coefficients and CIs can be found in online supplemental tables S2–S4. *The natural log of yearly SHS progression was used in the analysis. The models were corrected for the following covariates. Mean DAS28-ESR year 1: formal treatment, bDMARD, BL DAS28-ESR, years 2–3: mean RF/ACPA, early/established RA, BL DAS28-ESR. DAS remission year 1: remission type, bDMARD, early/established RA, BL DAS28-ESR, years 2–3: remission type, formal treatment, BL DAS28-ESR, years 4–6: remission type, symptom duration, BL DAS28-ESR. Mean SDAI/CDAI year 1: SDAI/CDAI, formal treatment, bDMARD, early/established RA, BL DAS28-ESR. SDAI/CDAI/Boolean remission year 1: remission type, formal treatment, early/established RA, BL DAS28-ESR, years 2–3: remission type, bDMARD, early/established, BL DAS28-ESR. SHS progression year 1: formal treatment, mean RF/ACPA, symptom duration, log(BL SHS), log(BL SHS)^2, years 2–3: mean RF/ACPA, log(BL SHS), log(BL SHS)^2. Mean HAQ year 1: bDMARD, early/established RA, BL HAQ, years 2–3: BL HAQ. ACPA, anticitrullinated protein antibody; bDMARD, biological disease-modifying antirheumatic drug; BL, baseline; CDAI, Clinical Disease Activity Index; DAS(28/44), Disease Activity Score (28/44 indicating the joint count); ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; LDA, low disease activity; RA, rheumatoid arthritis; REM, remission; RF, rheumatoid factor; SDAI, Simplified Disease Activity Index; SHS, Sharp van der Heijde Score; T2T, treat to target.

Subgroup analysis early versus established RA

After 1 year of T2T, targeting DAS-remission rather than DAS-LDA showed a numerical improvement in mean DAS for the subgroup with early RA (0.29, p=0.24), and this effect was more pronounced for established RA (1.21, p=0.25). The interaction between early versus established RA and the target was not significant (p=0.53). The percentage of patients in DAS-remission non-significantly improved when targeting DAS-remission (8%, p=0.16) or SDAI-CDAI LDA (4%, p=0.79) rather than DAS-LDA in the early RA subgroup. In the established RA subgroup, this effect was again more pronounced: DAS-remission versus DAS-LDA (20%, p=0.18), and significant for SDAI-CDAI LDA versus DAS-LDA (48%, p=0.003). The interaction term for the DAS-remission model was significant (p=0.01).

Subgroup analysis RCT versus cohort studies

The beneficial effects of SDAI/CDAI-LDA and DAS-remission compared with DAS-LDA were more pronounced in the cohort subgroups than in the RCT subgroups, when considering the outcomes mean DAS and HAQ at year 1, and DAS remission at years 1–3 (see online supplemental table S11). For the comparison of DAS-remission to DAS-LDA regarding SDAI/CDAI/Boolean remission at years 1–3, this effect was not present. None of the interaction terms were significant, except for mean HAQ year 1 (p=0.02).

Comparison of parsimonious and full models

The results of the parsimonious and full models were similar regarding the direction and statistical significance of the coefficients. The only exception was the improvement in the proportion of patients in DAS-remission when comparing the targets of DAS-remission (after 2–3 years of T2T) and SDAI/CDAI-LDA (after 1–3 years of T2T) to DAS-LDA: these did reach statistical significance in the parsimonious models, but were not statistically significant in the full models (see online supplemental tables S2–S7).

High RoB studies

As a sensitivity analysis, we ran the parsimonious models excluding the high RoB studies (see online supplemental table S1). The improvement in the proportion of patients in DAS-remission after 1 year of T2T when targeting DAS-remission versus DAS-LDA increased from 0.09 (p=0.11) to 0.11 (p=0.06). When targeting SDAI/CDAI-remission versus DAS-LDA, the improvement in the proportion of patients in DAS-remission remained 0.21 (p value from 0.04 to 0.03). Regarding mean HAQ after 1 year of T2T, there were no differences between targets, and this did not change when the high RoB study was excluded (DAS-remission target versus DAS-LDA from 0.00 (p=1.00) to 0.01 (p=0.82), SDAI/CDAI LDA target versus DAS-LDA from −0.03 (p=0.73) to −0.07 (p=0.58)).

Leave-one-out analyses

For the majority of the analyses, the direction and significance of the effect remained the same after performing leave-one-out analyses (see online supplemental table S12 for details).

Narrative results AEs and medication use

Insufficient data were available to perform meta-regression analysis of serious AE (S)AEs and medication use. Narratively, the percentages of patients with ≥1 reported AE at year 1 varied from 35% to 59% for the target DAS-LDA,[71 74 90] and from 82% to 96% for DAS-remission.[28 61] For SAEs at year 1, this varied from 5% to 19% for DAS-LDA,[48 74 90] from 0% to 19% for DAS-remission,[28 61 69] and from 2% to 15% for SDAI/CDAI LDA.[39 40] After 2 years of T2T, the SAEs for the target of DAS-LDA varied from 6% to 23%,[49 58 60] and from 0.6% to 18.4% for DAS-remission.[34 45 52] The reported use of bDMARDs during the first 1–2 years of T2T varied from 2% to 32% for the target DAS-LDA,[43 74] from 7% to 17% for DAS-remission,[52 73] and from 3% to 8% for SDAI-LDA.[76] After 5 years of T2T, SAEs varied from 5% to 21% for DAS-LDA,[79] and 17% was reported for the target DAS-remission.[56]

Narrative results target comparison studies

Two studies directly compared treatment targets. Tam et al found no significant differences after 1 year when targeting SDAI vs DAS28-ESR remission (mean change DAS28-ESR: −2.5(SD 1.3) vs −2.3(SD 1.3), p=0.51, mean change SDAI: −22.2(SD 12.6) vs −20.0(SD 11.8), p=0.35, median change in HAQ: −0.6(IQR −1.1 to −0.38) vs −0.5 (IQR −1.1 to 0.0, p=0.25), DAS remission (51% vs 55%, p=0.66), SDAI-remission: 37% vs 40%, p=0.73).[68] Hodkinson et al found no significant differences after 1 year when targeting SDAI-LDA vs CDAI-LDA (mean DAS28: 3.0 (SD 1.2) vs 3.3 (SD 1.2), p=0.29, DAS28-remission: 34% vs 33%, p=1.00, HAQ: 1.0 (SD 0.7) vs 1.0 (SD 0.7), p=0.94).[40]

DISCUSSION

In this study, we assessed the effect of different treatment targets on clinical and radiographic outcomes using meta-regression analyses. Our results indicate that aiming for SDAI/CDAI-LDA was superior to targeting DAS-LDA regarding the percentages of both DAS and SDAI/CDAI/Boolean remission. Aiming for SDAI/CDAI-LDA was also superior to targeting DAS-remission regarding SDAI/CDAI based outcomes (SDAI/CDAI/Boolean-remission and mean SDAI/CDAI). When comparing the target of DAS-remission to DAS-LDA, the former only significantly improved the percentage of patients in DAS-remission after 2–3 years of T2T, and only a trend was present for the improvement in DAS-remission at other time points and mean DAS28-ESR. Functioning and radiographic damage did not differ between targets.

A strength of the current study is that it is the first to perform a quantitative analysis of the optimal treatment

target based on the available evidence in literature. The technique of meta-regression allows to partly correct for heterogeneity between and within studies for measured confounders, thus optimally using the available evidence on T2T strategies in trials and cohort studies in RA. This resulted in the largest number of T2T cohorts and trials included in such a review to date.

Limitations of our study first include that our analyses are based on an indirect comparison of treatment targets. We aimed to correct for at least the most important confounders on study level, namely the availability of bDMARDs, the use of a formal treatment protocol, early versus established RA and the baseline value of the outcome. Nevertheless, residual confounding by insufficiently or unmeasured factors and treatment regimen specifics can certainly be present. Furthermore, insufficient data were available for the analysis of medication use, quality of life and AEs. These are important factors that should be taken into account when selecting a treatment target for a patient. Based on the limited reported evidence, we have no indication to assume that SAEs or the use of bDMARDs were increased for DAS-remission or SDAI/CDAI LDA versus DAS-LDA as a target, although the number of AEs may be higher for DAS-remission. However, as these results are from a small number of studies, and could not be adjusted for confounding, they should be interpreted with caution.

Further limitations include that information bias due to systematic differences in the scoring of the disease activity and/or SHS between studies could have occurred. Also, a certain amount of circularity is inherent to all studies evaluating a DAS based treatment target and outcome. For example, targeting DAS-remission may inherently increase the chance of achieving DAS-remission. Indeed in our results targets often performed better on related outcomes, although the target of SDAI/CDAI-LDA also performed better on DAS-based outcomes. No differences were observed in the more independent HAQ and SHS outcomes, which may be partly due to a limited variation in these measures with modern-day intensive therapy. Lastly, it is important to bear in mind that in routine clinical practice individual patient factors should always be considered. The optimal target is therefore a piece of the puzzle for clinical decision-making, but it is not a replacement of clinical decision-making for individual patients.

Interestingly, our results suggest a limited benefit of targeting DAS-remission compared with DAS-LDA. We unexpectedly even found a negative trend on the SHS-score when targeting DAS-remission compared with DAS-LDA, which could potentially be due to residual confounding. Based on previous studies, it could also be hypothesised that a stricter treatment target may cause premature drug cycling or reduced therapy adherence, both resulting in higher remaining disease activity.[60 93 94] Of note, the SHS is known to have a strong right-skewed distribution, making the mean more susceptible to outliers despite our efforts to compensate this with a natural log transformation. Unfortunately we could not analyse the effect of an SDAI/CDAI LDA target on the SHS outcome, as this was not reported.[39 40 76] Another finding of interest arose from our subgroup analysis of early versus established RA patients, where it seemed that targeting DAS-remission rather than DAS-LDA might be more beneficial for established RA than early RA patients. This may suggest that a less stringent target may be sufficient early in the disease, possibly in part because it allows for the effects of treatment adjustments to be fully established. Once a steady state has been reached, a stricter target may be required to optimise results. This is compatible with the ACR-recommendations on T2T, but in contrast with the advice of the international T2T task force.[5 14]

From the articles included in this review, two studies directly compared treatment targets. Tam *et al* found no difference between the SDAI and DAS28-ESR remission targets, a finding which we could not replicate in our study as this was the only article applying an SDAI-remission target.[68] Of note, the DMARD treatment protocol differed substantially between the two target arms, and this was not corrected for in the analysis. Hodkinson *et al* found no difference between the targets of SDAI- and CDAI-LDA, which may not be surprising given these targets are quite similar.[40] We, therefore, combined these uncommon targets in the current review.

Previous reviews have also considered the optimal target in a T2T strategy, although only narratively.[95 96] Hock *et al* report no preference for any particular target. Bergstra and Allaart conclude that based on the limited available and indirect evidence, aiming for remission rather than LDA (types not specified) seemed to result in more patients achieving remission, but not better physical functioning. This is in line with our results regarding DAS-remission as a target for treatment steering, but SDAI/CDAI-LDA targets appeared to be superior in several aspects as described above. Similar to Bergstra and Allaart, we found no effects on physical functioning as measured with the HAQ. This could potentially be due to the known 'floor-effect' of the HAQ, as it may be insensitive to changes at the lower end of the spectrum.[97]

The international T2T task force recommends to target a state of clinical remission, described as the absence of signs and symptoms of significant inflammatory disease.[5] They suggest that ACR-EULAR remission (ie, Boolean-remission or SDAI/CDAI-remission[10]) may be the best suitable definition for this criterion. Similarly, the EULAR guidelines recommend ACR-EULAR remission as the main therapeutic target, with LDA (type not specified) as an alternative, especially in established RA.[13] Surprisingly, no more than 1 of 66 T2T articles applied an SDAI-remission or Boolean remission target, and none applied a CDAI-remission target. This was insufficient for inclusion in our analyses, and therefore, our results cannot support these recommendations. The ACR guidelines, in contrast, recommend to initially target LDA, and to subsequently consider targeting remission (types

not specified).[14] Thus, there is no consensus in international guidelines regarding the initial treatment target, reflecting equipoise. Lastly, once a statisfactory stable level of disease activity has been reached after a period of T2T (perhaps irrespetive of whether the target was actually reached), tapering (b)DMARDs may be considered. As the ACR and EULAR guidelines differ regarding when to initiate tapering (being either remission or LDA), determining the optimal target may also be relevant in the context of tapering.[13 14]

To fully determine the optimal treatment target in a T2T strategy, an RCT comparing different targets head-to-head will be necessary. In line with our results and the ACR-guidelines, we would recommend to include an LDA target as a reference arm.[14] Based on our results SDAI-LDA or CDAI-LDA would be the LDA-target of choice, although DAS(28)-LDA may be an alternative as it is the most commonly used. In addition, DAS28-ESR remission may be considered, as our results showed a (limited) benefit of DAS-remission over DAS-LDA. Based on the EULAR and T2T task force guidelines, a target of SDAI or Boolean remission is of interest. Lastly, a predefined subgroup analysis regarding early versus established RA is recommended.

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