ORIGINAL RESEARCH

# Remission definitions guiding immunosuppressive therapy in rheumatoid arthritis: which is best fitted for the purpose?

Catia Duarte [1,2] Ricardo J O Ferreira [3,4] Paco M J Welsing,[5] Johannes W G Jacobs,[5] Laure Gossec [6,7] Pedro M Machado [8,9] Désirée van der Heijde [10] Jose Antonio Pereira da Silva [1,2]

## ABSTRACT

**Objective** To assess which definition of remission best predicts good radiographic outcome (GRO) and good functional outcome (GFO) in rheumatoid arthritis, focusing the updated American College of Rheumatology/European Alliance of Associations for Rheumatology criteria.

**Material and methods** Meta-analyses of individual patient data (IPD) from randomised controlled trials (RCTs). Six definitions of remission were considered: (1) Boolean with Patient Global Assessment (PGA)≤1 (Boolean); (2) Simplified Disease Activity Index (SDAI)≤3.3; (3) Clinical Disease Activity Index (CDAI)≤2.8; (4) Boolean with PGA≤2 (Updated-Boolean); (5) Boolean with Physician Global Assessment (PhGA≤1) replacing PGA (Boolean-PhGA) and (6) Boolean excluding PGA (3VBoolean). GRO was defined as a worsening ≤0.5 units in radiographic score and GFO as a no worsening in Health Assessment Questionnaire (HAQ), that is, ΔHAQ-DI≤0.0 units. Relationships between each remission definition at 6 and/or 12 months and GRO and GFO during the second year were analysed. Pooled probabilities for each outcome for each definition and their predictive accuracy were estimated.

**Results** IPD from eight RCTs (n=4423) were analysed. Boolean, SDAI, CDAI, Updated-Boolean, Boolean-PhGA and 3VBoolean were achieved by 24%, 27%, 28%, 32%, 33% and 43% of all patients, respectively. GRO among patients achieving remission ranged from 82.4% (3VBoolean) to 83.9% (SDAI). 3VBoolean showed the highest predictive accuracy for GRO: 51.1% versus 38.8% (Boolean) and 44.1% (Updated-Boolean). The relative risk of GFO ranged from 1.16 (Boolean) to 1.05 (3VBoolean). However, the proportion of GFO correctly predicted was highest for the 3VBoolean (50.3%) and lowest for the Boolean (43.8%).

**Conclusion** 3VBoolean definition provided the most accurate prediction of GRO and GFO, avoiding the risk of overtreatment in a substantial proportion of patients without increment in radiographic damage progression, supporting the proposal that 3VBoolean remission is preferable to guide immunosuppressive treatment. The patient's perspective, which must remain central, is best served by an additional patient-oriented target: a dual-target approach.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In 2011, a combined American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) initiative established the Simplified Disease Activity Index and the Boolean definitions of remission as the most adequate for clinical trials in rheumatoid arthritis (RA) and, together with Clinical Disease Activity Index, for clinical practice.

⇒ Prior research has demonstrated that a Patient Global Assessment (PGA)≤1 is the single most important factor impeding patients with RA from achieving remission. This near-remission status, which affects around 20% of all patients with RA in randomised controlled trials (RCTs) and practice cohorts, does not reflect subclinical inflammation and is not associated with increased radiographic damage accrual, thus putting patients at risk of immunosuppressive overtreatment.

⇒ In 2022, a new definition considering PGA≤2 as a criterion of remission was established by ACR/EULAR.

## WHAT THIS STUDY ADDS

⇒ This study shows that the rates of good radiographic outcome (GRO)—the ultimate objective of remission—associated with six different definitions were similar, but the rates of remission and thus, putative recommendations for incremental immunosuppression vary substantially.

⇒ The 3VBoolean remission definition (excluding PGA) results in the highest rate of remission and provides the most accurate predictor of both GRO and good functional outcome.

⇒ Compared with the Boolean and Updated-Boolean, the use of the 3VBoolean remission definition would avoid therapy escalation in 19% and in 11% of all these patients, respectively, without an increase in radiographic damage.

## INTRODUCTION

The current paradigm of rheumatoid arthritis (RA) management is epitomised by the

**HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY**

⇒ The 3VBoolean seems the most appropriate target definition to guide immunosuppressive therapy in clinical practice and to value medications in RCTs. Remission of impact (non-inflammatory disease burden) should be pursued in parallel, using informative patient-oriented targets: a dual-target approach.

treat-to-target (T2T) strategy, implying regular assessment of disease activity and treatment intensification with immunosuppressive drugs that have a disease-modifying anti-inflammatory effect (ie, disease-modifying anti-rheumatic drugs (DMARDs)), as needed to ensure that the target of remission (or at least low disease activity) is achieved as early and consistently as possible.[1–3]

In 2011, a joint initiative by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) established two provisional definitions of remission as the most adequate for use in clinical trials and clinical practice[4]: a Simplified Disease Activity Index (SDAI)≤3.3, or a Boolean-based definition requiring that swollen and tender 28-joint counts (SJC28 and TJC28), C reactive protein (CRP, mg/dL) and the Patient Global Assessment (PGA) of disease activity on a scale of 0–10 (=worst) are all ≤1. A third definition, a Clinical Disease Activity Index (CDAI)≤2.8 was also considered acceptable for clinical practice. Although these remission criteria were designed primarily for clinical trials, they have also been adopted as the primary target in treatment recommendations,[2 3 5] thus influencing clinical practice at a global level.

Over the last years, the inclusion of PGA in the target definitions and its cut-off in the Boolean criteria have raised controversy. PGA is only weakly correlated with disease activity[6] and essentially represents a measure of disease impact: pain, function, comorbidity, anxiety and depression are its strongest correlates.[6–8] Scoring PGA >1 is, by far, the most frequent reason why patients fail to meet Boolean remission criteria due to a single criterion. This, herein called 'PGA-near-remission' status has been shown to occur approximately in 1 of every 5 patients with RA, both in clinical trials and observational studies, representing 40%–60% of all patients otherwise in remission.[9 10]

These patients are put at risk of overtreatment with immunosuppressive therapy as they are free of (signs of) clinical or subclinical inflammation.[11–13] Based on individual patient data (IPD) meta-analysis from 11 randomised clinical trials (RCTs), we have shown that a PGA score >1 in patients who otherwise meet the Boolean remission criteria is not associated with increased radiographic joint damage accrual. Excluding PGA from the Boolean remission definition significantly improved its accuracy as a predictor of structural damage and physical function, and thus as a tool for guiding immunosuppression.[14]

Recently, the ACR/EULAR Boolean definition of remission has been changed by setting the PGA criterion cut-off at ≤2,[15 16] with the stated objective of increasing its agreement with SDAI-based remission criteria.[16] It has also been hypothesised that PGA might be better substituted by the Physician's Global Assessment (PhGA) of disease activity, based on its correlation with objective measures of inflammation, sensitivity to change and ability to correct for common confounders, such as infection and patient-reported outcomes.[17–22]

Therefore, we aimed to expand our previous study, and to test these newly proposed remission definitions, by assessing their impact on the rate of remission and its association with good radiographic and functional outcomes, the ultimate goals of T2T immunosuppressive therapy.

## METHODS
### Design and study selection
This was an IPD meta-analysis of published RCTs selected through a systematic literature review, as described elsewhere.[23] RCTs were included if testing the efficacy of biological DMARDs (bDMARDs) on ≥2 year radiographic outcomes in patients fulfilling the 1987 ACR or the 2010 ACR/EULAR criteria for RA,[24 25] with clinical, radiographic and functional data collection at baseline, 6, 12 and 24 months. RCTs with <2 years of follow-up, testing DMARDs dose spacing or suspension were excluded.

Only RCTs with available IPD were included in this analysis.

### Outcomes and remission definitions
#### Primary outcome
The primary outcomes were (1) the percentage of individuals with good radiographic outcome (GRO), defined as a change (Δ) ≤0.5 units in the van der Heijde modified total Sharp score (mTSS) during the second year of follow-up (ie, between months 12 and 24 of the trial) with the different definitions and (2) predictive accuracy of each definition for GRO. This ≤0.5 cut-off of GRO was preferred over the one used in the original ACR/EULAR study (ΔmTSS≤0.0) because 0.5 is considered the optimal cut-off if the average of two readers is used.[26 27]

#### Secondary outcome
The secondary outcomes were the percentage of individuals with good functional outcome (GFO), defined as no worsening, that is, ΔHAQ≤0.0 units in the Health Assessment Questionnaire-Disability Index (HAQ-DI) during the second year of follow-up (ie, between months 12 and 24 of the trial) and the predictive accuracy for GFO. We preferred this definition of GFO over the one used in the ACR/EULAR publication (ΔHAQ≤0 and HAQ≤0.5 at both time points),[4] which is believed to be too strict, as it represents a better outcome than expected for the general population.[9]

## Comparisons: definitions of remission

Six definitions of remission were assessed at 6 and 12 months in each RCT:

1. Boolean (reference): original 2011 ACR/EULAR Boolean definition: TJC28≤1, SJC28≤1, CRP (mg/dL)≤1 and PGA≤1.[4]
2. SDAI-remission: SDAI≤3.3.[28 29]
3. CDAI-remission: CDAI≤2.8.[29 30]
4. Updated-Boolean: the 2022 ACR/EULAR Boolean definition, only changing the Boolean in PGA≤2.[16]
5. Boolean-PhGA: only replacing the PGA criterion by PhGA≤1.
6. 3VBoolean: TJC28≤1, SJC28≤1, CRP≤1 mg/dL, that is, excluding the PGA.

These definitions are not mutually exclusive: patients may simultaneously meet several of them, for example, all patients in Boolean remission are also in updated-Boolean and in 3VBoolean, but the reverse is not true.

'For the primary analysis, each patient was classified as being in 'remission' if the corresponding remission criteria were satisfied at either the 6 months and/or the 12 months timepoints (ie, if a patient was in remission at 6 months, OR at 12 months OR at both time-points). We decided to use this composite timeframe of 6 and/or 12 months for remission to align with the original ACR/EULAR consensus work on the remission criteria.[4] Patients were classified according to the most stringent definition they satisfied (for instance, if a patient was in 4V-near-remission at 6 months and in 4V-remission at 12 months, he/she was classified as in 4V-remission).

### Data analyses and synthesis

Missing data were not imputed. We initially analysed each trial separately, irrespective of the treatment arm, to determine (1) the rate of remission per definition; (2) the rate of GRO and GFO for each definition; (3) rates of true positive (TP), that is, remission and GRO/GFO, true negative (TN), that is, non-remission and non-GRO/GFO, false positive (FP), that is, remission and non-GRO/GFO and false negative (FN), that is, non-remission and GRO/GFO; (4) accuracy as the percentage of patients with a correct prediction of having or not having GRO and GFO (TP+TN/(TP+TN+FP+FN));[30 31] (5) the relative risk (RR) (with 95% CI) of obtaining GRO and GFO for patients in remission versus non-remission for each definition; (6) the positive (LR+) and negative (LR−) likelihood ratios of meeting GRO and GFO as outcomes of each definition of remission. These were calculated based on the TP, TN, FP and FN results.

### Synthesis: meta-analyses

Direct comparison of the results of different remission definitions is impossible because definitions are not mutually exclusive. All results obtained from individual trials, as described above, were meta-analysed with the OpenMeta(Analyst) software (V.10.12), using the double arcsine transformation[32] and the DerSimonian-Laird random-effects method. For the meta-analysis of

likelihood ratios, we employed the hierarchical regression analysis of diagnostic data.[33] The $I^2$ of Higgins was calculated to quantify heterogeneity.[34] We also calculated the Net Reclassification Index (NRI).[35] An explanation of NRI and its results can be found in online supplemental file 2.

### Sensitivity analysis

Mean radiographic change and percentage of patients with a radiographic change >5 (considered high progression), both during the second year of follow-up (ie, from months 12 to 24), were also assessed as outcomes of mutually exclusive Boolean remission states to enable direct comparison. These states were Boolean remission, PGA-Near-Remission (3VBoolean+PGA>1) and 3V-Non-remission (SJC28>1 AND/OR TJC28>1 AND/OR CRP>1 mg/dL), at 6 and/or 12 months in all cases.

## RESULTS

### Studies and participants

From the total of identified studies (n=27), only 8 RCTs[31–38] were included in the final analyses. Reasons for non-inclusion of 16 RCTs were reported in a prior report,[9] and 3 studies, all testing golimumab, were now also excluded because data were not made available anymore in the same platform. Similar rates of remission, GRO and GFO were observed in the current and our previous report with 11 RCTs. These trials included patients with varying disease duration, most having established disease and inadequate response to methotrexate (table 1).

Among the 6392 patients included in the eight trials, 1969 patients were excluded because of missing information on the remission definition and/or on the primary outcome. Characteristics of the included patients (n=4423) and trials are described in table 1. Excluded patients had slightly higher age, and higher PGA, PhGA and HAQ scores at baseline than included patients (online supplemental table S1).

### Frequency of remission status and good outcomes

Taking all treatment arms together, the pooled meta-analytic percentage of remission at 6 and/or 12 months was 24.3% using the Boolean definition, 27.3% for SDAI, 27.9% for CDAI, 32.4% for Updated Boolean, 33.3% for Boolean-PhGA and 43.4% for 3VBoolean (table 2). GRO was observed in 77.6% of all patients, ranging from 65% to 91% in different trials, and GFO in 70.5% (65.4% to 76.3%), table 2.

### Association between remission status and good outcomes

Among patients who met the respective remission definition, GRO percentages varied from 82.4% for the 3VBoolean definition to 83.9% for SDAI, without statistically significant differences between the six definitions. For patients not in remission, GRO rate varied from 72.4% to 76.3% (table 3). The rates of GRO in remission versus those in non-remission were statistically

**Table 1** Baseline features of the 4423 patients from the eight RCTs included in the analysis

| Trial name (year of publication) | DE019[31] (2004) | TEMPO[32] (2004) | COMET[33] (2008) | RAPID 1[34] (2008) | RAPID 2[35] (2009) | LITHE[36] (2011) | DE013[37] (2013) | FUNCTION[38] (2016) |
|---|---|---|---|---|---|---|---|---|
| Biologic agent | Adalimumab | Etanercept | Etanercept | Certolizumab | Certolizumab | Tocilizumab | Adalimumab | Tocilizumab |
| RA population | MTX-IR | csDMARD-IR* | MTX-naive | MTX-IR | MTX-IR | MTX-IR | MTX-naive | MTX-naive |
| N patients randomised | 619 | 686 | 542 | 982 | 619 | 1196 | 799 | 1162 |
| N pts. available for this IPD study | 619 | 684 | 542 | 857 | 582 | 1147 | 799 | 1162 |
| N (%) included in analyses† | 425 (69) | 442 (64) | 344 (64) | 650 (76) | 417 (72) | 761 (66) | 540 (68) | 844 (60) |
| **Demographics** | | | | | | | | |
| Female (%) | 75 | 76 | 74 | 82 | 81 | 83 | 74 | 80 |
| Age, years | 55.4 (12.0) | 51.9 (12.5) | 51.7 (13.7) | -‡ | -‡ | 52.2 (12.3) | 52.2 (13.4) | 49.9 (12.9) |
| RA duration, years | 10.8 (9.0) | 6.3 (5.0) | 7.4 (5.4) | 6.3 (4.3) | 6.0 (4.1) | 9.5 (8.0) | 0.7 (0.8) | 0.5 (0.5) |
| RF positive (%) | 85 | 66 | 96 | 84 | 77 | 79 | 85 | 90 |
| **Disease activity** | | | | | | | | |
| DAS28CRP3v | 4.9 (0.7) | 5.3 (0.8) | 4.9 (0.9) | 5.3 (0.7) | 5.2 (0.7) | 4.8 (1.0) | 5.3 (0.8) | 4.9 (0.9) |
| CRP (mg/dL) | 1.8 (1.9) | 2.7 (3.1) | 3.6 (3.6) | 2.5 (2.7) | 2.4 (2.5) | 2.2 (2.5) | 3.8 (3.9) | 2.5 (2.9) |
| TJC28 | 14.5 (6.4) | 18.0 (6.7) | 13.8 (7.1) | 17.7 (6.1) | 17.9 (6.4) | 14.8 (7.5) | 16.8 (6.3) | 15.8 (7.3) |
| SJC28 | 13.2 (5.5) | 15.0 (5.8) | 12.0 (6.2) | 14.8 (5.4) | 14.3 (5.6) | 11.5 (6.2) | 14.4 (5.7) | 11.7 (6.0) |
| PGA (0–10cm) | 5.2 (2.2) | 6.9 (1.7)§ | 6.5 (1.9)§ | 6.3 (1.9) | 6.0 (2.1) | 5.9 (2.4) | 6.4 (2.4) | 6.5 (2.2) |
| PhGA (0–10cm) | 6.1 (1.7) | 6.6 (1.5)§ | 6.5 (1.5)§ | 6.3 (1.5) | 6.4 (1.4) | 5.9 (2.4) | 6.5 (1.8) | 6.3 (1.8) |
| **Functional status (HAQ-DI)** | | | | | | | | |
| Baseline score | 1.4 (1.4) | 1.7 (0.6) | 1.6 (1.6) | 1.6 (0.6) | 1.6 (0.6) | 1.4 (0.6) | 1.5 (0.6) | 1.5 (0.7) |
| **Radiographic joint scores¶** | | | | | | | | |
| Baseline score | 69.0 (55.8) | 35.7 (49.7) | 8.4 (16.2) | 48.2 (57.1) | 34.2 (46.3) | 30.3 (30.9) | 19.9 (21.0) | 5.9 (14.5) |

All results are presented as mean (SD), unless stated otherwise.
*Other than methotrexate.
†Only patients who have information on the remission definition and on the primary outcome were included.
‡Data regarding age were not available in RAPID 1 and RAPID 2 due to regulatory changes occurred since the initial data analyses.
§Assessed with numeric rating scale (0–10) and not with visual analogue scale (0–10cm).
¶All trials used Sharp van der Heijde mTSS (0–448) except in the LITHE trial, in which Genant mTSS (0–202) was used instead.
CRP, C reactive protein; csDMARD, Conventional synthetic disease-modifying anti-rheumatic drug; DAS28CRP3v, Disease Activity Score with 28-joint counts, using C reactive protein and 3 variables; HAQ-DI, Health Assessment Questionnaire-Disability Index; IPD, individual patient data; IR, insufficient responder; mTSS, modified total Sharp score; MTX, methotrexate; PGA, Patient Global Assessment; PhGA, Physician Global Assessment; RA, rheumatoid arthritis; RCTs, randomised controlled trials; RF, rheumatoid factor; SJC28, swollen 28-joint counts; TJC28, tender 28-joint counts.

**Table 2** Frequency of remission and good outcomes in the eight included studies

| Trial (year) | N* | Remission at 6 and/or 12 months, n (%) | | | | | | Good radiographic outcome during the second year of follow-up, n (%) | Good functional outcome during the second year of follow-up, n (%) | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | Boolean | SDAI | CDAI | Updated-Boolean | Boolean-PhGA | 3VBoolean | ΔmTSS≤0.5 | N† | ΔHAQ≤0.0 |
| DE019 (2004) | 425 | 68 (16.0) | 63 (14.8) | 74 (17.4) | 94 (22.1) | 79 (18.6) | 113 (26.6) | 297 (69.9) | 398 | 281 (70.6) |
| TEMPO (2006) | 442 | 113 (25.6) | 101 (22.9) | 103 (23.3) | 156 (35.3) | 154 (34.8) | 204 (46.2) | 330 (74.7) | 421 | 300 (71.3) |
| COMET (2008) | 344 | 102 (29.7) | 103 (29.9) | 108 (31.4) | 143 (41.6) | 190 (55.2) | 209 (60.8) | 289 (84.0) | 324 | 237 (73.1) |
| RAPID 1 (2008) | 650 | 177 (27.2) | 225 (34.6) | 227 (34.9) | 243 (37.4) | 232 (35.7) | 320 (49.2) | 508 (78.2) | 642 | 420 (65.4) |
| RAPID 2 (2009) | 417 | 51 (12.2) | 70 (16.8) | 74 (17.7) | 77 (18.5) | 85 (20.4) | 132 (31.7) | 324 (77.7) | 435 | 290 (66.7) |
| LITHE (2011) | 761 | 141 (18.5) | 180 (23.7) | 169 (22.2) | 209 (27.5) | 186 (24.4) | 307 (40.3) | 610 (80.2) | 519 | 346 (66.7) |
| DE013 (2013) | 540 | 156 (28.9) | 178 (33.0) | 188 (34.8) | 175 (32.4) | 179 (33.1) | 206 (38.1) | 351 (65.0) | 518 | 383 (73.9) |
| FUNCTION (2016) | 844 | 308 (36.5) | 362 (42.9) | 352 (41.7) | 381 (45.1) | 377 (44.7) | 459 (54.4) | 766 (90.8) | 616 | 470 (76.3) |
| Total | **4423** | 1116 | 1282 | 1295 | 1478 | 1482 | 1950 | 3475 | 3873 | 2727 |
| Meta-analytic % (95% CI) | | 24.3 (18.4 to 30.2) | 27.3* (20.4 to 34.4) | 27.9* (21.4 to 34.4) | 32.4* (25.8 to 39.0) | 33.3* (25.3 to 41.3) | 43.4* (35.8 to 50.9) | 77.6 (71.4 to 83.9) | | 70.5 (67.6 to 73.5) |

Boolean-remission: 2011 ACR/EULAR Boolean definition: TJC28≤1, SJC28≤1, CRP (mg/dL)≤1 and PGA≤1; SDAI-remission: SDAI≤3.3; CDAI-remission: CDAI≤2.8; Updated Boolean-remission: 2022 ACR/EULAR Boolean definition, with PGA≤2.0; Boolean-PhGA-remission: TJC28≤1, SJC28≤1, CRP≤1 mg/dL and PhGA≤1; 3VBoolean-remission: TJC28≤1, SJC28≤1, CRP≤1 mg/dL.

*Number of patients with available data both on remission and radiographic outcome. All meta-analyses used the double arcsine transformation.[60] ΔmTSS: change in the modified total Sharp score during the second year of follow-up, ΔHAQ-DI: change in Health Assessment Questionnaire-disability index. *p<0.001 when compared with Boolean-remission definition.

†Number of patients with HAQ-DI reported among those included in the primary analysis.

ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; EULAR, European Alliance of Associations for Rheumatology; PGA, Patient Global Assessment; PhGA, Physician's Global Assessment; SDAI, Simplified Disease Activity Index; SJC28, swollen 28-joint counts; TJC28, tender 28-joint counts.

**Table 3** Frequency of good radiographic (n=4423) and functional (n=3873) outcomes in patients in remission versus those not in remission, for each definition

| Definition | | GRO, ∆mTSS≤0.5 | GFO, ∆HAQ≤0 |
|---|---|---|---|
| Boolean | Remission | 83.1 (77.9 to 88.3) | 77.4 (74 to 80.9) |
| | Non-remission | 76.3 (69.6 to 83.0) | 67.2 (64 to 70.3) |
| SDAI | Remission | 83.9 (79.0 to 88.7) | 76.3 (72.5 to 80.1) |
| | Non-remission | 75.6 (68.8 to 82.3) | 68.1 (65.7 to 70.5) |
| CDAI | Remission | 83.1 (77.9 to 88.3) | 76.0 (72.1 to 80.0) |
| | Non-remission | 75.7 (68.8 to 82.6) | 68.1 (65.7 to 70.5) |
| Updated-Boolean | Remission | 82.8 (77.7 to 88.0) | 73.8 (69.2 to 78.4) |
| | Non-remission | 75.3 (68.7 to 82.0) | 68.6 (66.2 to 70.9) |
| Boolean-PhGA | Remission | 83.1 (78.5 to 87.7) | 74.8 (71.5 to 78.0) |
| | Non-remission | 75.3 (68.5 to 82.1) | 68.2 (65.5 to 70.9) |
| 3VBoolean | Remission | 82.4 (77.5 to 87.3) | 72.7 (69.2 to 76.3) |
| | Non-remission | 72.4 (67.7 to 77.2) | 69.2 (66.0 to 72.3) |

Boolean-remission: 2011 ACR/EULAR Boolean definition: TJC28≤1, SJC28≤1, CRP (mg/dL)≤1 and PGA≤1; SDAI-remission: SDAI≤3.3; CDAI-remission: CDAI≤2.8; Updated-Boolean remission: 2022 ACR/EULAR Boolean definition, with PGA≤2.0; Boolean-PhGA-remission: TJC28≤1, SJC28≤1, CRP≤1 mg/dL and PhGA≤1; 3VBoolean-remission: TJC28≤1, SJC28≤1, CRP≤1 mg/dL.
ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; EULAR, European Alliance of Associations for Rheumatology; GFO, good functional outcome; GRO, good radiographic outcome; PGA, Patient Global Assessment; PhGA, Physician's Global Assessment; SDAI, Simplified Disease Activity Index; SJC28, swollen 28-joint counts; TJC28, tender 28-joint counts; ∆HAQ, change in Health Assessment Questionnaire; ∆mTSS, change in the modified total Sharp score.

significantly different for all definitions. However, due to the small absolute differences, relative risk ratios were low, ranging from 1.09 to 1.10 (figure 1).

Among patients with non-GRO, the mean radiographic progression during the second year of follow-up was 3.2 (95% CI: 2.6 to 3.9) with 15.8% of these patients having a ∆mTSS>5 (data not shown).

GFO in patients who met the respective remission definition varied from 72.7% (3VBoolean) to 77.4% (Boolean), the difference between these two being statistically significant (p=0.02), table 3. Patients meeting a remission definition had a statistically significant higher probability of achieving GFO when compared with patients in non-remission, irrespective of the definition used. Risk ratios varied from 1.05 to 1.16, being higher for definitions including PGA (online supplemental figure S1).

### Likelihood ratios of GRO and GFO for the different remission definitions

The likelihood ratio of having good radiographic outcome with versus without remission (LR+) was the highest (ie, clinically desirable) for SDAI (1.41) and lowest for the 3VBoolean definition (1.29). There was, however, an overlap between the 95% CI for all definitions. Conversely, the likelihood of having GRO in the absence of remission (LR−) was lower (desirable) for 3VBoolean (0.85) and higher for Boolean-PhGA and Updated-Boolean remission (0.88 and 0.89, respectively). LR− was not statistically significant different for Boolean, CDAI and SDAI remission (table 4).

LR+ for GFO was highest with Boolean (1.34), and lowest with 3VBoolean-remission (1.08). LR− (GFO not

being inf remission) only reached statistical significance for Boolean-PhGA (0.88) and SDAI remission (0.89). There were large overlaps between 95% CI between definitions, in all cases.

### Accuracy of prediction

The percentage of patients whose GRO was accurately predicted on the basis of remission status (TP+TN) was low with all definitions, varying from 38.8% (Boolean) to 51.1% (3VBoolean); the remaining definitions performed intermediately (table 5). The accuracy percentages of SDAI and CDAI were 41.5% and 41.1%; those of Boolean-PhGA and Updated-Boolean 44.8% and 44.1%, respectively. The higher accuracy of 3V remission is essentially a result of a substantially lower FN%, that is, patients who failed remission but still had GRO.

The percentage of correctly predicted GFO was again highest for the 3VBoolean (50.3%) and lowest for Boolean (43.8%); the remaining definitions performed intermediately (online supplemental table S2).

### Sensitivity analysis

The mean meta-analysed radiographic change (∆mTSS) during the second year of follow-up was calculated in mutually exclusive Boolean-based remission states, to enable direct comparison: Boolean: 0.17, PGA-Near-Remission (3VBoolean-remission+PGA>1): 0.17 and 3V-Non–remission (SJC28 AND/OR TJC28 AND/OR CRP>1): 0.64. The percentage of patients with a radiographic change >5 was 1.5%, 2.5% and 4.5%, respectively, see online supplemental table S3.
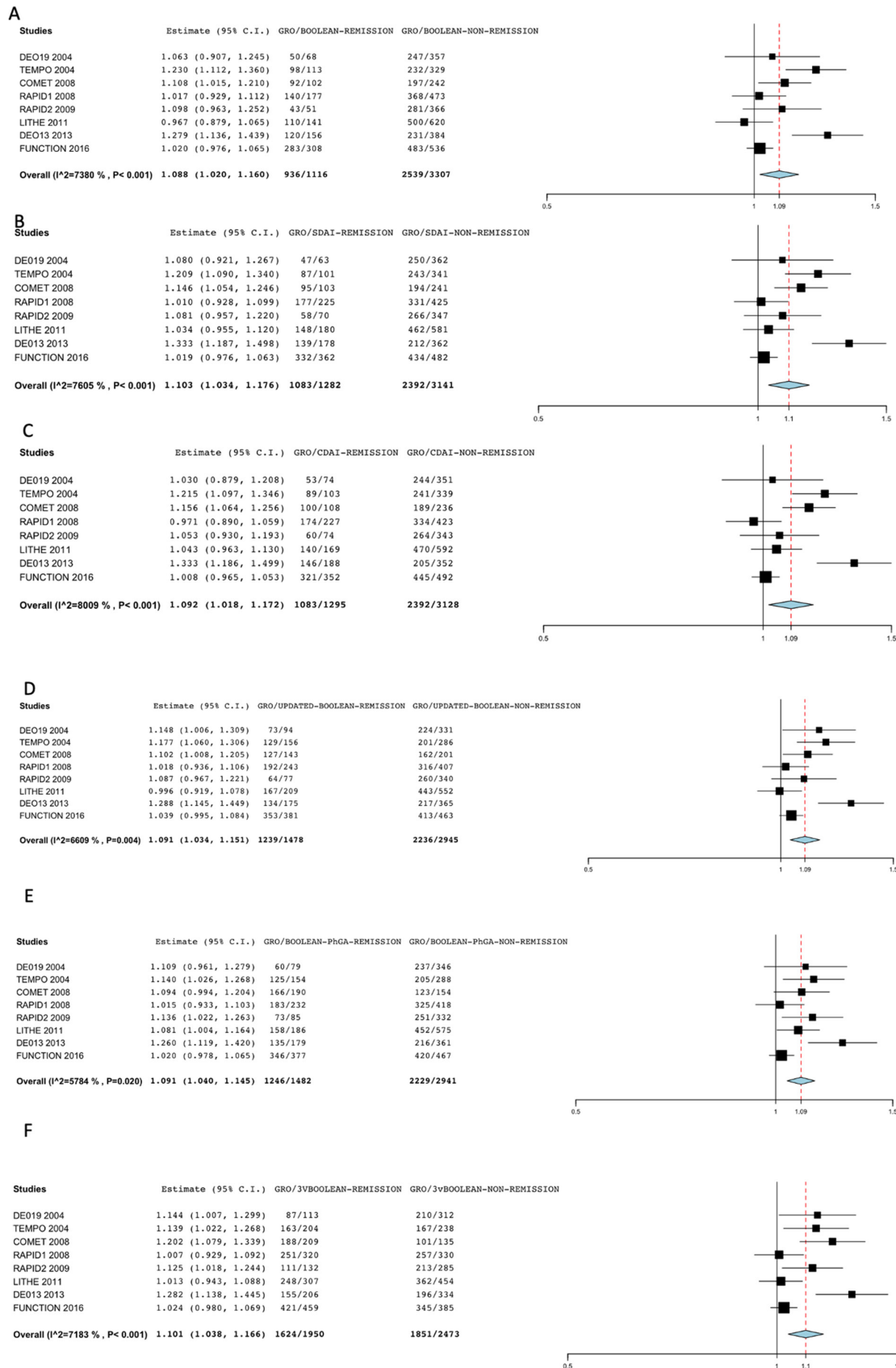
**Figure 1** Meta-analysis of risk ratio of obtaining good radiographic outcome (ΔmTSS≤0.5) for patients in remission versus non-remission, per definition. (A) Boolean remission; (B) SDAI remission; (C) CDAI remission; (D) Updated-Boolean remission; (E) Boolean-PhGA remission and (F) 3VBoolean remission. CDAI, Clinical Disease Activity Index; GRO, good radiographic outcome; ΔmTSS, change in the modified total Sharp score; PhGA, Physician's Global Assessment; SDAI, Simplified Disease Activity Index.

**Table 4** Meta-analysed likelihood ratios (95% CI) for good radiographic (n=4423) and functional (n=3873) outcomes for the different definitions of remission

| Remission definition | GRO, ΔmTSS≤0.5 | | | GFO, ΔHAQ≤0 | | |
|---|---|---|---|---|---|---|
| | LR+ | LR− | $I^2$ LR+ $I^2$ LR− | LR+ | LR− | $I^2$ LR+ $I^2$ LR− |
| Boolean | 1.34 (1.07 to 1.68) | 0.92 (0.80 to 1.06) | 56% 0% | 1.34 (1.15 to 1.54) | 0.90 (0.79 to 1.02) | 21% 0% |
| SDAI | 1.41 (1.13 to 1.74) | 0.90 (0.79 to 1.03) | 67.9% 0% | 1.26 (1.13 to 1.41) | 0.89 (0.80 to 0.99) | 2.3% 0% |
| CDAI | 1.34 (1.05 to 1.71) | 0.93 (0.83 to 1.05) | 69.6% 0% | 1.27 (1.06 to 1.52) | 0.92 (0.83 to 1.03) | 1.8% 0% |
| Updated-Boolean | 1.33 (1.13 to 1.57) | 0.89 (0.79 to 0.99) | 45.6% 0% | 1.16 (1.03 to 1.3) | 0.91 (0.83 to 1.01) | 23.4% 0% |
| Boolean-PhGA | 1.32 (1.16 to 1.50) | 0.88 (0.78 to 0.98) | 12.5% 0% | 1.19 (1.08 to 1.30) | 0.88 (0.80 to 0.96) | 16.7% 0% |
| 3VBoolean | 1.29 (1.11 to 1.49) | 0.85 (0.76 to 0.95) | 57.9% 29.1% | 1.08 (1.0 to 1.18) | 0.94 (0.88 to 1.02) | 17.6% 0% |

LR+: positive likelihood ratio, sensitivity/(1−specificity); LR−: negative likelihood ratio, (1−sensitivity)/specificity; ΔmTSS: change in the modified total Sharp score during the second year of follow-up, ΔHAQ-DI: change in Health Assessment Questionnaire-Disability Index; $I^2$: $I^2$ of Higgins to quantify heterogeneity.
Boolean-remission: 2011 ACR/EULAR Boolean definition: TJC28≤1, SJC28≤1, CRP (mg/dL) ≤1 and PGA≤1; SDAI-remission: SDAI≤3.3; CDAI-remission: CDAI≤2.8; Updated-Boolean remission: 2022 ACR/EULAR Boolean definition, with PGA≤2.0; Boolean-PhGA-remission: TJC28≤1, SJC28≤1, CRP≤1 mg/dL and PhGA≤1; 3VBoolean-remission: TJC28≤1, SJC28≤1, CRP≤1 mg/dL.
ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CRP, C reactive protein; EULAR, European Alliance of Associations for Rheumatology; GFO, good functional outcome; GRO, good radiographic outcome; LR+, positive likelihood ratio; LR−, negative likelihood ratio; PGA, Patient Global Assessment; PhGA, Physician's Global Assessment; SDAI, Simplified Disease Activity Index; SJC28, swollen 28-joint counts; TJC28, tender 28-joint counts; ΔHAQ, change in Health Assessment Questionnaire; ΔmTSS, change in the modified total Sharp score.

## DISCUSSION

In our previous study, we showed that omitting PGA from the original 2011 ACR/EULAR Boolean definition (Boolean) increased its validity in guiding RA immunosuppressive therapy.[9] This present study, including data from 8 out of 11 previous RCTs, confirms and expands these findings by showing that the probabilities of GRO as outcome of all six different constructs of remission, including the 2022 ACR/EULAR Boolean definition (Updated-Boolean) and the Boolean-PhGA, are very similar (82.4% to 83.9%). In contrast, the percentages of patients meeting each of the six remission constructs vary considerably, from 24.3% (Boolean) to 43.4% (3VBoolean). These results clearly illustrate that the adoption of the 3VBoolean definition as a treatment target would avoid unnecessary increments of immunosuppressive therapy, that is, additional treatment without further reduction in structural damage, in a substantial proportion of patients in comparison to all five alternative definitions. It should be noted that meeting even the strictest definition (Boolean) does not guarantee radiographic stability: 16.9% of these patients still have some progression, although modest.

Although all remission definitions perform poorly as predictors of the outcome GRO, correct classification (TP+TN) rates varied from 38.8% with Boolean to 51.1% with 3VBoolean definition, with an intermediate rate of 44.1% for Updated-Boolean. Substituting PGA by PhGA (Boolean-PhGA) would result in an overall performance similar to that of updated-Boolean, in all aspects examined.

These data must be considered in the context of the included clinical trials in our research with an average percentage of GRO as high as 77.6%, including all treatments and both arms in each trial. This is in agreement with the trend for lower progression of joint damage observed in recent decades,[39 40] and supports the argument for a less stringent definition of the treatment target, in addition to arguments of costs and risks of (unnecessary) medication.[41 42]

Results regarding GFO show a similar trend. GFO was observed in 70.5% of all participants and the ability of the different definitions of remission to predict this outcome was generally poor. However, our results must be interpreted considering that we decided to define GFO as no deterioration in HAQ without demanding a maximum HAQ of 0.5 at the end of the follow-up, as required in the ACR/EULAR original study.[4] We believe that is more appropriate for populations with longstanding RA, as the one included in this study. The ACR/EULAR definition has been considered too demanding, even for the general population.[43] We wanted, otherwise, to keep the definition closest to the ACR /EULAR, allowing people with no change to be considered as having GFO. Most people with active disease under effective treatment will have some improvement in HAQ.

The definitions including the PGA have a higher positive likelihood of good functional outcomes, which may militate against the remotion of PGA from Boolean remission. However, it is important to notice the strong correlation between PGA and self-reported function, irrespective of disease activity,[6 8 17] as well the influence

**Table 5** Meta-analytic pooled prediction accuracy of different remission status for the good radiographic (GRO, n=4423) outcomes

| | | Boolean remission | | | | | Updated-Boolean remission | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Yes | No | Total | | | Yes | No | Total |
| GRO, ΔmTSS≤0.5 | Yes | 20.3 TP (14.7–25.9) | 57.2 FN (51.9–62.5) | 77.6 (71.4–83.9) | GRO, ΔmTSS≤0.5 | Yes | 27.0 TP (20.6–33.5) | 50.5 FN (45.6–55.3) | 77.6 (71.4–83.9) |
| | No | 3.9 FP (2.9–4.9) | 18.4 TN (12.4–24.1) | 22.4 (16.1–28.6) | | No | 5.3 FP (4.0–6.5) | 17.0 TN (11.6–22.3) | 22.4 (16.1–28.6) |
| | Total | 24.3 (18.4–30.2) | 75.7 (69.8–81.6) | 38.8 (34.1–43.5) | | Total | 32.4 (25.8–39.0) | 67.6 (61.0–74.2) | 44.1 (39.9–48.5) |
| | | SDAI remission | | | | | Boolean-PhGA remission | | |
| | | Yes | No | Total | | | Yes | No | Total |
| GRO, ΔmTSS≤0.5 | Yes | 23.0 TP (16.5–29.5) | 54.5 FN (49.2–59.8) | 77.6 (71.4–83.9) | GRO, ΔmTSS≤0.5 | Yes | 27.8 TP (20.5–35.1) | 49.7 FN (44.0–55.4) | 77.6 (71.4–83.9) |
| | No | 4.2 FP (3.0–5.3) | 18.3 TN (12.3–24.3) | 22.4 (16.1–28.6) | | No | 5.3 FP (3.9–6.7) | 9 TN (11.3–22.4) | 22.4 (16.1–28.6) |
| | Total | 27.3 (20.4–34.2) | 72.7 (65.8–79.6) | 41.5 (37.1–48.5) | | Total | 33.3 (25.3–41.3) | 66.7 (58.7–74.7) | 44.8 (40.1–49.4) |
| | | CDAI remission | | | | | 3VBoolean remission | | |
| | | Yes | No | Total | | | Yes | No | Total |
| GRO, ΔmTSS≤0.5 | Yes | 23.2 TP (17.1–29.4) | 54.2 FN (48.7–59.7) | 77.6 (71.4–83.9) | GRO, ΔmTSS≤0.5 | Yes | 36.0 TP (28.3–43.7) | 41.5 FN (36.8–46.1) | 77.6 (71.4–83.9) |
| | No | 4.5 FP (3.2–5.8) | 17.7 TN (12.0–23.4) | 22.4 (16.1–28.6) | | No | 7.3 FP (5.6–8.9) | 15.0 TN (9.9–20.0) | 22.4 (16.1–28.6) |
| | Total | 27.9 (21.4–34.4) | 72.1 (65.6–78.6) | 41.1 (36.5–45.6) | | Total | 43.4 (35.8–50.9) | 56.6 (49.1–64.2) | 51.1 (46.7–55.6) |

The sum of meta-analytic percentages is slightly less than 100% due to error estimations of multi-category prevalence. The double arcsine transformation is the preferred method in all meta-analyses used.[60]
Accurately predicted=TP+TN. Between brackets is the pooled 95% CI.
CDAI, Clinical Disease Activity Index; FN, false negative; FP, false positive; GRO, good radiographic outcome; SDAI, Simplified Disease Activity Index; TN, true negative; TP, true positive; ΔmTSS, change in the modified total Sharp score.

of several factors besides disease activity on function, including pain, ageing, comorbidities and socioeconomic status,[44–47] which are not amenable to immunosuppressive therapy. Moreover, likelihood ratios of patients for the outcome GFO for updated Boolean and 3VBoolean remission were not statistically significantly different, the latter being associated with the highest accuracy in the prediction of GFO, although it was only 50.3%. All these findings, associated with well-known limitations of PGA,[48–50] support our proposal to remove PGA from the assessment of disease activity used to guide immunosuppressive therapy.

The findings of this study must be considered in light of some limitations and strengths. The use of IPD of over 4000 patients and their inclusion in stringent RCT conditions are important strengths. This study does not include the newest RCTs, particularly considering new drugs such as Jak inhibitors, but the RCTs included were similar to the ones used by ACR/EULAR task forces.[15 16] The definition of remission was based only on two timepoints (6 and/or 12 months), mirroring the ACR/EULAR methodology. It is always debatable which time points should be chosen when analysing longitudinal data and exploring a link between an earlier time point and a later one. Since disease activity varies and data collection is usually discontinuous, an arbitrary decision must be made. In the present work, we chose to use status at 6 and/or 12 months as our binary definition of remission because this was the definition initially used by ACR/EULAR to develop the remission criteria.[4] Other analyses with more repeated and closely spaced assessments would be valuable, but they are not currently feasible with existing datasets. Data were derived from RCTs, which may question the applicability of the results to real-world patients. Recognisably, retrospective data obtained from RCTs do not necessarily apply to real-world clinical settings, especially taking into account the strict inclusion/exclusion criteria of RCTs. Furthermore, our finding that a specific remission state is associated with better outcomes does not mean that aiming at this specific remission state would result in better treatment outcomes. An observational study, with data from an early disease cohort, showed similar results to current ones,[51] but our observations need further prospective evaluation in clinical settings.

In some RCTs,[33 36 38] patients may have changed or intensified treatment after 12 months if remission was not achieved: the potential impact of these changes on the outcome is not accounted for. Our study was designed to evaluate the predictive capacity of each definition of remission for GRO and GFO and not its ability to discriminate between active treatment and placebo. Therefore, our data were analysed regardless of the treatment arm, which could have some impact, although probably minor, on the results. The included trials differ in baseline characteristics, namely disease duration and treatment, that may influence the outcomes. In our study, subgroup analyses were not performed because the current use of a target to guide therapy requires the use of a broad definition capable of serving the diverse populations seen in clinical practice, as opposed to the specific inclusion criteria used in individual RCTs. However, we have previously shown that these baseline features and the treatment arm do not significantly change the significant conclusions of such analyses.[9] There is evidence that bDMARDs are associated with more suppression of radiographic progression, compared with MTX, at comparable levels of disease activity.[52] There are also strong suggestions that individual bDMARDs and tsDMARDs may have differential effects not only on bone destruction but also on pain or fatigue, independent of the control of inflammation.[53] These differences may, naturally, have a diverse influence on remission rates, with different definitions and their relationship with radiographic and functional outcomes. The same is true regarding disease duration at treatment initiation.[54] These factors deserve to be the object of future studies gathering large numbers of patients with early and later diseases treated with different agents. It should be noted, however, that these differences suggest, if anything, that aiming at less strict remission states would also be adequate from the structural and functional point of view, in line with our study conclusions.

It should be noted that 31% of patients were excluded due to missing data. These patients had higher mean PGA and HAQ-DI scores, but they were not significantly different with regard to other factors known as relevant for radiographic outcomes, such as joint counts, CRP, rheumatoid factor positivity and disease duration. This makes it unlikely, though not impossible, that the exclusion of these patients may have relevantly changed the relationship we found between disease activity status and the outcomes under consideration.

Our findings have important implications for clinical practice. Real-world data regarding the actual incidence and consequences of overtreatment in trials and current practice are scarce and debatable.[13 55] In the current data set, this risk would affect 11.1% to 19.3% of all patients: the extra patients classified as (possibly) needing to intensify treatment (ie, not being in remission) by the different definitions of remission versus 3v-remission. We believe these findings raise important questions on overtreatment in the context of the efficacy/safety balance of currently available drugs. These patients could see their treatment intensified despite gaining no further inhibition of radiographic progression. The concern addressed in our paper is that current treatment recommendations may actually favour overtreatment by recommending additional immunosuppression to patients whose inflammatory process is already under control. This study further supports our previous proposal that using the 3VBoolean remission, that is, excluding PGA, might significantly reduce the risk of overtreatment, as enticed by the current treatment recommendations and deserves further evaluation, preferably in a clinical trial, as target to guide immunosuppressive treatment.

This proposal has been criticised on the basis that it would ignore the patient's perspectives and needs. However, reducing the risk of unnecessary therapy is certainly addressing important patients' needs. Furthermore, we proposed that the 3VBoolean definition is adopted in the context of a Dual-Target strategy, that is, pursuing, in parallel, a second target focused on disease impact from the patient's perspective.[56 57] These two targets are not strictly independent: pursuing remission will also substantially decrease disease impact in most, though not all, patients. If impact is not substantially reduced once patients achieve or approach biological remission, special attention should be given to the unabated domains of disease impact.[58] These are not made clear by the use of PGA: a more detailed and informative tool would be required. The EULAR's RA Impact of Disease, particularly considering each of its seven numerical rating scales separately,[59] seems particularly well positioned to serve this purpose, but other Patient Reported Outcome Measures (PROMs) could be considered.

In conclusion, this study suggests that among six definitions of remission, including the original and the updated ACR/EULAR Boolean definitions, the 3VBoolean remission definition may deserve preference as a target guide for immunosuppressive therapy in a T2T strategy. In fact, it would likely reduce the risk of overtreatment attributable to PGA, without increasing the occurrence of relevant radiographic damage (or functional impairment). Diminishing disease impact from the patient's perspective is best served by a dedicated independent treatment target pursued in parallel. This is the core of the Dual-Target strategy. We believe it deserves to be further tested, preferably in a clinical trial.

**Author affiliations**
[1]Department of Rheumatology, Centro Hospitalar e Universitario de Coimbra EPE, Coimbra, Portugal
[2]Institute for Clinical and Biomedical Research, University of Coimbra, Coimbra, Portugal
[3]Nursing Research, Innovation and Development Centre of Lisbon (CIDNUR), Higher School of Nursing of Lisbon, Lisboa, Portugal
[4]Health Sciences Research Unit: Nursing (UICiSA:E), Higher School of Nursing of Coimbra, Coimbra, Portugal
[5]Department of Rheumatology and Clinical Immunology, Utrecht University, Utrecht, The Netherlands
[6]INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Sorbonne Universite, Paris, France

[7]Department of Rheumatology, APHP, Hopital Universitaire Pitie Salpetriere, Paris, France

[8]Department of Neuromuscular Diseases, MRC Centre for Neuromuscular Diseases, University College London, London, UK

[9]Department of Rheumatology, Northwick Park Hospital, London North West University Healthcare NHS Trust, London, UK

[10]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands

**Twitter** Catia Duarte @Catiacmduarte, Ricardo J O Ferreira @FerreiraRJO and Pedro M Machado @pedrommcmachado

**ORCID iDs**
Catia Duarte http://orcid.org/0000-0001-9327-6935
Ricardo J O Ferreira http://orcid.org/0000-0002-2517-0247
Laure Gossec http://orcid.org/0000-0002-4528-310X
Pedro M Machado http://orcid.org/0000-0002-8411-7972
Désirée van der Heijde http://orcid.org/0000-0002-5781-158X
Jose Antonio Pereira da Silva http://orcid.org/0000-0002-2782-6780

## REFERENCES

1. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 2016;75:3–15.
2. Fraenkel L, Bathon JM, England BR, et al. American college of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2021;73:1108–23. 10.1002/art.41752 Available: https://acrjournals.onlinelibrary.wiley.com/toc/23265205/73/7
3. Smolen JS, Landewé RBM, Bergstra SA, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying Antirheumatic drugs: 2022 update. *Ann Rheum Dis* 2023;82:3–18.
4. Felson DT, Smolen JS, Wells G, et al. American college of rheumatology/European League against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis* 2011;70:404–13.
5. Smolen JS, Aletaha D, Bijlsma JWJ, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010;69:631–7.
6. Ferreira RJO, Dougados M, Kirwan JR, et al. Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients. *Rheumatology (Oxford)* 2017;56:1573–8.
7. Radner H, Yoshida K, Tedeschi S, et al. Different rating of global rheumatoid arthritis disease activity in rheumatoid arthritis patients with multiple morbidities. *Arthritis Rheumatol* 2017;69:720–7.
8. Ferreira RJO, Duarte C, Ndosi M, et al. Suppressing inflammation in rheumatoid arthritis: does patient global assessment blur the target? A practice-based call for a paradigm change. *Arthritis Care Res (Hoboken)* 2018;70:369–78.
9. Ferreira RJO, Welsing PMJ, Jacobs JWG, et al. Revisiting the use of remission criteria for rheumatoid arthritis by excluding patient global assessment: an individual meta-analysis of 5792 patients. *Ann Rheum Dis* 2021;80:293–303.
10. Ferreira RJO, Santos E, Gossec L, et al. The patient global assessment in RA Precludes the majority of patients otherwise in remission to reach this status in clinical practice. *Semin Arthritis Rheum* 2020;50:583–5.
11. Brites L, Rovisco J, Costa F, et al. High patient global assessment scores in patients with rheumatoid arthritis otherwise in remission do not reflect Subclinical inflammation. *Joint Bone Spine* 2021;88:S1297-319X(21)00115-9.
12. Nakabo S, Tsuji Y, Inagaki M, et al. Severe joint deformity and patient global assessment of disease are associated with discrepancies between Sonographic and clinical remission: A cross-sectional study of rheumatoid arthritis patients. *Mod Rheumatol* 2021;31:334–42.
13. Paulshus Sundlisæter N, Sundin U, Aga A-B, et al. Inflammation and biologic therapy in patients with rheumatoid arthritis achieving versus not achieving ACR/EULAR Boolean remission in a treat-to-target study. *RMD Open* 2022;8:e002013.
14. Navarro-Compán V, Gherghe AM, Smolen JS, et al. Relationship between disease activity indices and their individual components and radiographic progression in RA: a systematic literature review. *Rheumatology (Oxford)* 2015;54:994–1007.
15. Studenic P, Felson D, de Wit M, et al. Testing different thresholds for patient global assessment in defining remission for rheumatoid arthritis: are the current ACR/EULAR Boolean criteria optimal *Ann Rheum Dis* 2020;79:445–52.
16. Studenic P, Aletaha D, de Wit M, et al. American college of rheumatology/EULAR remission criteria for rheumatoid arthritis: 2022 revision. *Ann Rheum Dis* 2023;82:74–80.
17. Desthieux C, Hermet A, Granger B, et al. Patient-physician Discordance in global assessment in rheumatoid arthritis: A systematic literature review with meta-analysis. *Arthritis Care Res (Hoboken)* 2016;68:1767–73.
18. Brites L, Dinis de Freitas J, Costa F, et al. Patient-physician Discordance in assessment of disease activity in rheumatoid arthritis patients. *Acta Reumatol Port* 2021;46:103–9.
19. Tago M, Sawada T, Nishiyama S, et al. Influence of large joint involvement on patient-physician Discordance in global assessment of rheumatoid arthritis disease activity analyzed by a novel joint index. *Int J Rheum Dis* 2018;21:1237–45.
20. Guimarães MFBR, Pinto MR da C, Resende GG, et al. Discordance between the patient's and physician's global assessment in rheumatoid arthritis: data from the REAL study-Brazil. *PLoS One* 2020;15:e0230317.
21. Pazmino S, Lovik A, Boonen A, et al. Does including pain, fatigue, and physical function when assessing patients with early rheumatoid arthritis provide a comprehensive picture of disease burden *J Rheumatol* 2021;48:174–8.

22 Pyne L, Bykerk VP, Boire G, *et al*. Increasing treatment in early rheumatoid arthritis is not determined by the disease activity score but by physician global assessment: results from the CATCH study. *J Rheumatol* 2012;39:2081–7.

23 Ferreira RJO, Welsing PMJ, Gossec L, *et al*. The impact of patient global assessment in the definition of remission as a Predictor of long-term radiographic damage in patients with rheumatoid arthritis: protocol for an individual patient data meta-analysis. *Acta Reumatol Port* 2018;43:52–60.

24 Arnett FC, Edworthy SM, Bloch DA, *et al*. The American rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.

25 Aletaha D, Neogi T, Silman AJ, *et al*. Rheumatoid arthritis classification criteria: an American college of rheumatology/ European League against rheumatism collaborative initiative. *Arthritis Rheum* 2010;62:2569–81.

26 Ory PA. Interpreting radiographic data in rheumatoid arthritis. *Ann Rheum Dis* 2003;62:597–604.

27 van der Heijde D, Simon L, Smolen J, *et al*. How to report radiographic data in randomized clinical trials in rheumatoid arthritis: guidelines from a Roundtable discussion. *Arthritis Rheum* 2002;47:215–8.

28 Smolen JS, Aletaha D. Patients with rheumatoid arthritis in clinical care. *Ann Rheum Dis* 2004;63:221–5.

29 Aletaha D, Ward MM, Machold KP, *et al*. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity States. *Arthritis Rheum* 2005;52:2625–36.

30 Aletaha D, Nell VPK, Stamm T, *et al*. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. *Arthritis Res Ther* 2005;7:R796–806.

31 Keystone EC, Kavanaugh AF, Sharp JT, *et al*. Radiographic, clinical, and functional outcomes of treatment with Adalimumab (a human anti-tumor necrosis factor Monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004;50:1400–11.

32 van der Heijde D, Klareskog L, Rodriguez-Valverde V, *et al*. Comparison of Etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum* 2006;54:1063–74.

33 Emery P, Breedveld FC, Hall S, *et al*. Comparison of methotrexate monotherapy with a combination of methotrexate and Etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 2008;372:375–82.

34 Keystone E, Heijde D van der, Mason D Jr, *et al*. Certolizumab Pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 2008;58:3319–29.

35 Smolen J, Landewé RB, Mease P, *et al*. Efficacy and safety of Certolizumab Pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis* 2009;68:797–804.

36 Fleischmann RM, Halland A-M, Brzosko M, *et al*. Tocilizumab inhibits structural joint damage and improves physical function in patients with rheumatoid arthritis and inadequate responses to methotrexate: LITHE study 2-year results. *J Rheumatol* 2013;40:113–26.

37 Breedveld FC, Weisman MH, Kavanaugh AF, *et al*. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with Adalimumab plus methotrexate versus methotrexate alone or Adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006;54:26–37.

38 Burmester GR, Rigby WF, van Vollenhoven RF, *et al*. Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. *Ann Rheum Dis* 2016;75:1081–91.

39 Rahman MU, Buchanan J, Doyle MK, *et al*. Changes in patient characteristics in anti-tumour necrosis factor clinical trials for rheumatoid arthritis: results of an analysis of the literature over the past 16 years. *Ann Rheum Dis* 2011;70:1631–40.

40 Park Y-J, Gherghe AM, van der Heijde D. Radiographic progression in clinical trials in rheumatoid arthritis: a systemic literature review of trials performed by industry. *RMD Open* 2020;6:e001277.

41 Landewé RBM. Overdiagnosis and Overtreatment in rheumatology: a little caution is in order. *Ann Rheum Dis* 2018;77:1394–6.

42 Ramiro S, Landewé R, van der Heijde D, *et al*. Stricter treat-to-target in RA does not result in less radiographic progression: a longitudinal analysis in RA BIODAM. *Rheumatology (Oxford)* 2023;62:2989–97.

43 Sokka T, Kautiainen H, Hannonen P, *et al*. Changes in health assessment questionnaire disability scores over five years in patients with rheumatoid arthritis compared with the general population. *Arthritis Rheum* 2006;54:3113–8.

44 Karpouzas GA, Dolatabadi S, Moran R, *et al*. Correlates and predictors of disability in vulnerable US Hispanics with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2012;64:1274–81.

45 Luque Ramos A, Redeker I, Hoffmann F, *et al*. Comorbidities in patients with rheumatoid arthritis and their association with patient-reported outcomes: results of claims data linked to questionnaire survey. *J Rheumatol* 2019;46:564–71.

46 Kapetanovic MC, Lindqvist E, Nilsson J, *et al*. Development of functional impairment and disability in rheumatoid arthritis patients followed for 20 years: relation to disease activity, joint damage, and Comorbidity. *Arthritis Care & Research* 2015;67:340–8. 10.1002/acr.22458 Available: https://acrjournals.onlinelibrary.wiley.com/toc/21514658/67/3

47 Izadi Z, Li J, Evans M, *et al*. Socioeconomic disparities in functional status in a national sample of patients with rheumatoid arthritis. *JAMA Netw Open* 2021;4:e2119400.

48 Nikiphorou E, Radner H, Chatzidionysiou K, *et al*. Patient global assessment in measuring disease activity in rheumatoid arthritis: a review of the literature. *Arthritis Res Ther* 2016;18:251.

49 Ferreira RJO, Eugénio G, Ndosi M, *et al*. "Influence of the different "patient global assessment" formulations on disease activity score by different indices in rheumatoid arthritis". *Clin Rheumatol* 2018;37:1963–9.

50 Ferreira RJO, de Wit M, Henriques M, *et al*. It can't be zero!' difficulties in completing patient global assessment in rheumatoid arthritis: a mixed methods study. *Rheumatology (Oxford)* 2020;59:1137–47.

51 Ferreira RJO, Fautrel B, Saraux A, *et al*. Patient global assessment of disease activity and radiographic progression in early arthritis: three-year results from the ESPOIR cohort. *Arthritis Care Res (Hoboken)* 2021;73:1300–5.

52 Favalli EG, Becciolini A, Biggioggero M. Structural integrity versus radiographic progression in rheumatoid arthritis. *RMD Open* 2015;1:e000064.

53 Landewé RBM, Sepriano A, Bergstra SA. WHY most (but perhaps not all) Dmards work equally well. *Semin Arthritis Rheum* 2023;2023:S0049-0172(23)00158-0.

54 van Nies JAB, Krabben A, Schoones JW, *et al*. What is the evidence for the presence of a therapeutic window of opportunity in rheumatoid arthritis? A systematic literature review. *Ann Rheum Dis* 2014;73:861–70.

55 Chakr RM da S, Brenol C, Ranzolin A, *et al*. Rheumatoid arthritis seems to have DMARD treatment decision influenced by Fibromyalgia. *Rev Bras Reumatol Engl Ed* 2017;57:403–11.

56 Ferreira RJO, Ndosi M, de Wit M, *et al*. Dual target strategy: a proposal to mitigate the risk of Overtreatment and enhance patient satisfaction in rheumatoid arthritis. *Ann Rheum Dis* 2019;78:e109.

57 Duarte C, Ferreira RJO, Santos EJF, *et al*. Treating-to-target in rheumatology: theory and practice. *Best Pract Res Clin Rheumatol* 2022;36:S1521-6942(21)00077-2.

58 Nagy G, Roodenrijs NMT, Welsing PMJ, *et al*. EULAR points to consider for the management of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 2022;81:20–33.

59 Duarte C, Santos EJF, Ferreira RJO, *et al*. Validity and reliability of the EULAR instrument RAID.7 as a tool to assess individual domains of impact of disease in rheumatoid arthritis: a cross-sectional study of 671 patients. *RMD Open* 2021;7:e001539.

60 Barendregt JJ, Doi SA, Lee YY, *et al*. Meta-analysis of prevalence. *J Epidemiol Community Health* 2013;67:974–8.