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Achievement of Remission in Two Early Rheumatoid Arthritis Cohorts Implementing Different Treat-to-Target Strategies

Vibeke Norvang,[1] Gina H. Brinkmann,[2] Kazuki Yoshida,[3] Siri Lillegraven,[4] Anna-Birgitte Aga,[4] Joseph Sexton,[4] Sara K. Tedeschi,[3] Houchen Lyu,[5] Ellen S. Norli,[6] Till Uhlig,[1] Tore K. Kvien,[1] Maria D. Mjaavatten,[4] Daniel H. Solomon,[3] and Espen A. Haavardsholm,[4] the ARCTIC Trial Group and the NOR-VEAC Study Group

Objective. The objective of this study was to compare achievement of remission in 2 early rheumatoid arthritis (RA) treat-to-target (TTT) cohorts, a tight control cohort with a target of stringent remission in a randomized controlled trial and an observational cohort targeting a looser definition of remission in clinical practice.

Methods. We analyzed data from the Aiming for Remission in Rheumatoid Arthritis: a randomised trial examining the benefit of ultrasound in a Clinical Tight Control regimen (ARCTIC) trial and the Norwegian Very Early Arthritis Clinic (NOR-VEAC) observational study. Both were Norwegian multicenter studies that included disease-modifying antirheumatic drug (DMARD)–naive RA patients and implemented TTT. The target in the ARCTIC trial was remission defined as a Disease Activity Score (DAS) of <1.6 plus 0 swollen joints on a 44-joint count, while the target in the NOR-VEAC study was the less stringent remission target of a DAS28 of <2.6. We assessed achievement of the study-specific targets and compared the odds of achieving the American College of Rheumatology(ACR)/European League Against Rheumatism (EULAR) Boolean remission during 2 years of follow-up.

Results. We included 189 patients from the ARCTIC trial and 330 patients from the NOR-VEAC study. The study-specific target had been achieved in more than half of the patients in each cohort at 6 months, increasing to >60% at 12 and 24 months. The odds of achieving ACR/EULAR Boolean remission during follow-up were higher in the ARCTIC trial than in the NOR-VEAC study, with significant differences at 3 months (odds ratio 1.73 [95% confidence interval 1.03–2.89]), 12 months (odds ratio 1.97 [95% confidence interval 1.21–3.20]), and 24 months (odds ratio 1.82 [95% confidence interval 1.05–3.16]).

Conclusion. A majority of patients in both cohorts reached the study-specific treatment targets. More patients in the ARCTIC trial than in the NOR-VEAC study achieved ACR/EULAR Boolean remission during follow-up, suggesting that targeting a more stringent definition of remission provides further potential for favorable outcomes of a TTT strategy.

INTRODUCTION

Treat-to-target (TTT) strategies have become a cornerstone in the care of patients with rheumatoid arthritis (RA) (1,2). Key elements of a TTT strategy include defining a treatment target when initiating a new drug therapy, close monitoring of treatment response, and intensification of treatment if the target is not reached (1). A TTT approach has consistently shown favorable outcomes compared to conventional care (3,4) and is included in current treatment recommendations from the American College

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[1]Vibeke Norvang, MD, Till Uhlig, MD, PhD, Tore K. Kvien, MD, PhD: Diakonhjemmet Hospital and University of Oslo, Oslo, Norway; [2]Gina H. Brinkmann, MD, PhD: Østfold Hospital, Grålum, Norway; [3]Kazuki Yoshida, MD, ScD, Sara K. Tedeschi, MD, Daniel H. Solomon, MD, MPH: Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts; [4]Siri Lillegraven, MD, PhD, MPH, Anna-Birgitte Aga, MD, PhD, Joseph Sexton, PhD, Maria D. Mjaavatten, MD, PhD, Espen A. Haavardsholm, MD, PhD: Diakonhjemmet Hospital, Oslo, Norway; [5]Houchen Lyu, MD, PhD: Brigham and Women´s Hospital, Boston, Massachusetts; [6]Ellen S. Norli, MD, PhD: Martina Hansens Hospital, Sandvika, Norway.

Drs. Solomon and Haavardsholm contributed equally to this work.

of Rheumatology (ACR) (5) and the European League Against Rheumatism (EULAR) (6). However, despite the known benefits and recommendations, TTT strategies are still inadequately implemented in clinical practice for a variety of reasons (7–9), and many patients continue to have moderate or high disease activity despite treatment with disease-modifying antirheumatic drugs (DMARDs) (10,11). Identifying successful strategies for incorporating TTT into routine care is crucial for improving RA outcomes.

The evidence base for TTT in RA mainly consists of randomized controlled trials (RCTs) comparing a TTT strategy with conventional care or studies comparing the outcomes of TTT implemented in RCTs or observational cohorts with conventional care in clinical practice (3,4). No previous study has made a head-to-head comparison of a TTT strategy in an RCT versus a TTT strategy in an observational cohort. This analytic approach may lead to a better understanding of what factors are important for achieving the treatment target and how to improve the incorporation of TTT in clinical practice.

The preferred treatment target in a TTT strategy in RA is a state of sustained clinical remission (1). Different composite disease activity indices or criteria may be used to define remission, and the frequency of patients reaching remission depends on the definition used (12,13). Current TTT recommendations suggest defining remission using the ACR/EULAR Boolean criteria, the Clinical Disease Activity Index (CDAI), or the Simplified Disease Activity Index (1,14). Remission according to these definitions allows for limited remaining disease activity and is associated with the prevention of joint destruction, improved functional outcomes, and a reduced risk of comorbidities (13,15). While several studies have compared the outcomes of having achieved different disease activity states or remission according to different criteria (13,16–18), limited data exist on the impacts of targeting different definitions of remission in a TTT strategy (19).

The objective of the present study was to compare the achievement of remission during 2 years of follow-up in 2 early RA cohorts implementing different TTT strategies. For this purpose, we used data from 2 Norwegian multicenter TTT studies of DMARD–naive RA patients: the Aiming for Remission in Rheumatoid Arthritis: a randomised trial examining the benefit of ultrasound in a Clinical Tight Control regimen (ARCTIC) trial (20) and the Norwegian Very Early Arthritis Clinic (NOR-VEAC) observational study (21). We assessed achievement of the study-specific remission target in each cohort and examined whether the tight control TTT strategy with a target of stringent remission in the ARCTIC trial led to achievement of the ACR/EULAR Boolean remission in more patients compared to the TTT approach targeting a less stringent definition of remission in the NOR-VEAC study.

PATIENTS AND METHODS

Study design. A list of the ARCTIC trial and NOR-VEAC study investigators is shown in Appendix A. The ARCTIC trial (20) (ClinicalTrials.gov identifier: NCT01205854) compared the outcomes of an ultrasound TTT strategy with a conventional TTT strategy in patients with early RA. The target in both arms was stringent remission, defined as a Disease Activity Score (DAS) (22,23) of <1.6 plus 0 swollen joints on a 44-joint count, with the additional requirement of no power Doppler ultrasound activity in the ultrasound group. A total of 230 DMARD-naive RA patients were included at 11 rheumatology centers across Norway between 2010 and 2013. The main inclusion criteria were age 18–75 years, fulfillment of the 2010 ACR/EULAR classification criteria for RA (24), <2 years since the first patient-reported swollen joint, and indication for start of DMARD therapy without prior DMARD use. All patients provided written informed consent, and the trial was conducted in compliance with the Declaration of Helsinki. Patients were followed up for 2 years, with visits at baseline and after 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, and 24 months. Treatment for all patients followed a predefined protocol, starting with methotrexate (MTX) monotherapy in combination with tapering doses of prednisolone. Subsequent escalation in patients who had poor improvement in disease activity and had not reached the target included optimizing the dosage of MTX to 25–30 mg/week, synthetic DMARD triple therapy, and biologic therapy. Treatment for patients with high disease activity and risk factors for progressive joint destruction (anti–cyclic citrullinated peptide [anti-CCP] or rheumatoid factor [RF] positivity, and either erosions on computed radiography or baseline RA magnetic resonance imaging bone marrow edema score of >2) could be escalated directly to biologic therapy if initial therapy with MTX failed. Overviews of the treatment algorithm and the decision rules for escalation of therapy in the ARCTIC trial are found in Supplementary Tables 1 and 2 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41232/abstract).

The NOR-VEAC study (21) was a multicenter prospective observational study implementing a TTT approach in patients with early RA initiating DMARD therapy. The target was remission defined as a DAS28 of <2.6 (23,25). A total of 429 patients with early RA were included at 6 rheumatology centers in southeastern Norway between 2010 and 2016. The main inclusion criteria for patients starting follow-up according to TTT principles

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Address correspondence to Vibeke Norvang, MD, Diakonhjemmet Hospital, PO Box 23 Vinderen, 0319 Oslo, Norway. E-mail: v.norvang@gmail.com.

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were ages 18–75 years, <12 months since the first patient-reported swollen joint, a clinical diagnosis of RA, and indication for DMARD therapy without prior DMARD use. All patients provided written informed consent, and the study was conducted in compliance with the Declaration of Helsinki. Patients initiating DMARD therapy were scheduled to have monthly follow-up visits until the target of DAS28 remission had been reached. Further follow-up was scheduled every 3 months up to 24 months and, if still at target, every 6 months up to a total of 5 years. The study protocol did not include a specific treatment algorithm; however, participating centers committed to treat patients according to current EULAR recommendations for the management of RA, following TTT principles (26–28). The EULAR recommendations suggested initiating MTX as the first-line DMARD and rapidly increasing the dosage to 20–30 mg/week. Further escalation of therapy to either another synthetic DMARD regimen or to a biologic DMARD was to be guided by the presence or absence of poor prognostic factors, such as RF or anti-CCP positivity, high levels of disease activity, or early erosions. Short-term glucocorticoid treatment was recommended as part of the initial therapy.

For inclusion of patients from the ARCTIC trial and the NOR-VEAC study into the current analyses, we applied a set of common eligibility criteria: RA patients ages 18–75 years who fulfilled the 2010 ACR/EULAR classification criteria for RA (24), who were DMARD-naive, and who had started MTX monotherapy within 31 days of a study visit and had at least one follow-up visit (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41232/abstract). Although the inclusion criteria for the NOR-VEAC study allowed for a maximum of 12 months since the first patient-reported swollen joint at the time of study enrollment, some patients were followed up for a period of time before initiating DMARD therapy. For inclusion into the current analyses, we allowed for a maximum of 13 months from the first patient-reported swollen joint to the time the first DMARD therapy was initiated.

Ethics approval. The ARCTIC trial and the NOR-VEAC study were approved by an independent ethics committee (the Regional Committee for Medical and Health Research Ethics South East; reference no. 2010/744 and reference no. 2010/719, respectively).

Standardization of study visits. The visits scheduled according to the study protocols were fairly similar in the 2 cohorts. However, the implemented study visits were more frequent in the ARCTIC trial than in the NOR-VEAC study. Further, visits in the NOR-VEAC study occurred with highly varying frequency, both within patients and between patients. In order to compare outcomes, we standardized the follow-up schedules by specifying certain time points of interest (3, 6, 12, and 24 months) and allowing the inclusion of observations within a time window of 2 months before or after the ideal visit date. For the 3-month time point only, we used observations within 1 month before or after the ideal time point. If a patient had >1 observation within the time window for a visit of interest, the observation closest to the ideal time point was selected for analyses.

Outcome assessments. The main outcomes were 1) achievement of the study-specific treatment targets, and 2) achievement of remission as defined by the ACR/EULAR Boolean criteria (14). Both outcome measures were assessed after 3, 6, 12, and 24 months.

Study-specific targets were defined as 1) DAS <1.6 (22,23) plus 0 swollen joints on a 44-joint count in the ARCTIC trial, and 2) DAS28 <2.6 (25) in the NOR-VEAC study. ACR/EULAR Boolean remission was defined as a score of ≤1 for the following: swollen joint count (SJC), tender joint count (TJC), C-reactive protein (CRP) level (mg/dl), and patient global assessment of disease (14). For the calculation of ACR/EULAR Boolean remission, we used a 28-joint count, which was calculated in both cohorts.

In additional analyses, we assessed disease activity during follow-up according to the CDAI, defining remission as CDAI ≤2.8, low disease activity as CDAI >2.8 and ≤10, moderate disease activity as CDAI >10 and ≤22, and high disease activity as CDAI >22 (29,30).

Statistical analysis. To balance the 2 cohorts on baseline covariates, we used inverse probability of treatment weights using the propensity scores (31). The propensity score is defined as the probability of being assigned to a specific group or treatment conditional on the observed covariates (32). The propensity scores were calculated by fitting a multivariable logistic regression model, including variables considered to be potential confounders in the estimation of the main outcome (see Supplementary Text, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41232/abstract). Inverse probability of treatment weights using the propensity score assigns a weight to each subject based on the inverse propensity score and creates a weighted cohort (pseudo-population) in which observed confounders have been balanced between the 2 treatment groups (31). The weighted sample was used for further analyses of the outcome. We assessed the adequacy of the specification of the model by examining the degree of balancing of baseline covariates between the 2 cohorts, comparing means and prevalence, and comparing the distribution of continuous variables (31) (Table 1 and Supplementary Figures 2 and 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41232/abstract).

We used descriptive statistics to evaluate the proportion of patients reaching the study-specific remission targets as well as the disease activity states according to the CDAI during follow-up. To compare achievement of the ACR/EULAR Boolean remission in longitudinal analyses, we combined baseline balancing using

Table 1. Baseline characteristics before and after propensity score weighting using inverse probability of treatment weights*

Characteristic	Observed cohorts		Propensity score–weighted cohorts		
	ARCTIC trial (n = 189)	NOR-VEAC study (n = 330)	ARCTIC trial (n = 183)	NOR-VEAC study (n = 277)	Standardized mean difference†
Age, years	51.1 ± 13.9	53.8 ± 13.7	52.5 ± 13.3	53.1 ±14.2	−0.046
Female, %	61.4	66.1	65.2	62.8	0.049
Anti-CCP positivity, %	82.0	75.5	78.9	79.1	−0.008
Rheumatoid factor positivity, %	71.4	63.3	66.8	67.4	−0.014
Time since first patient-reported swollen joint, months	5.5 ± 3.5	4.5 ± 2.8	4.8 ± 3.3	4.8 ± 3.0	−0.001
Presence of ≥1 comorbidity, %	52.9	51.8	52.8	54.9	−0.043
Body mass index, kg/m^2	25.5 ± 4.4	25.8 ± 4.5	25.6 ± 4.4	25.6 ± 4.3	0.008
Current smoker, %	21.7	24.2	23.1	22.1	0.023
University/college degree, %	41.8	49.7	49.8	49.8	0.001
Full-time employment, %	35.4	35.5	36.0	37.6	−0.034
CRP level, mg/liter	16.2 ± 22.3	19.5 ± 25.8	17.4 ± 23.9	18.0 ± 24.3	−0.025
ESR, mm Hg	25.2 ± 19.1	27.9 ± 20.5	26.6 ± 20.0	26.4 ± 19.6	0.012
SJC28	7.2 ± 5.6	6.3 ± 5.2	6.8 ± 5.5	6.8 ± 5.4	−0.003
TJC28	7.1 ± 5.0	6.7 ± 5.6	6.8 ± 5.0	6.9 ± 5.6	−0.025
Physician global assessment (0–100 mm VAS)	41.5 ± 20.6	41.1 ± 19.6	41.6 ± 21.1	41.8 ± 20.1	−0.008
Patient global assessment (0–100 mm VAS)	50.5 ± 23.8	49.4 ± 24.8	50.2 ± 24.4	49.7 ± 23.9	0.022
SDAI	25.2 ± 12.8	24.1 ± 13.3	24.5 ± 12.9	24.6 ± 13.7	−0.002
DAS28	4.8 ± 1.3	4.7 ± 1.3	4.8 ± 1.3	4.8 ± 1.3	−0.003
EQ-5D	0.51 ± 0.29	0.49 ± 0.31	0.49 ± 0.30	0.50 ± 0.30	−0.027
RAID	4.55 ± 2.09	4.52 ± 2.21	4.54 ± 2.15	4.49 ± 2.17	0.025

* Except where indicated otherwise, values are the mean ± SD. ARCTIC = Aiming for Remission in Rheumatoid Arthritis: a randomised trial examining the benefit of ultrasound in a Clinical Tight Control regimen; NOR-VEAC = Norwegian Very Early Arthritis Clinic; anti-CCP = anti–cyclic citrullinated peptide; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; SJC28 = swollen joint count in 28 joints; TJC28 = tender joint count in 28 joints; VAS = visual analog scale; SDAI = Simplified Disease Activity Index; DAS28 = Disease Activity Score in 28 joints; EQ-5D = EuroQol-5 dimensions; RAID = Rheumatoid Arthritis Impact of Disease.
† After propensity score weighting.

inverse probability of treatment weights with methods to account for imbalances in missing data between the 2 cohorts during follow-up. Missing data in the ARCTIC trial were almost exclusively a result of missing visits due to dropout. The dropout rate in the ARCTIC trial was 6.9% at 12 months and 10.6% at 24 months. Missing data in the NOR-VEAC study were a result of missing variables at existing visits, missing visits in patients with subsequent follow-up visits (i.e., intermittent missing visits), or missing visits due to dropout. The overall amount of missing outcome data in the NOR-VEAC study was 21.2% at 12 months and 35.6% at 24 months.

We applied a combination of methods to account for missing data, assuming a missing at random mechanism (33). First, we used multiple imputation by chained equations to impute missing variables at existing visits in the NOR-VEAC study (34,35). We used the full data set (n = 330) to impute the following covariates if missing: CRP, erythrocyte sedimentation rate (ESR), patient global assessment of disease, SJC28, and TJC28. Second, we used a strict censoring approach to account for intermittent missing visits by censoring each patient at the first missing visit as recommended by Robins et al (36). Finally, we used inverse probability of censoring weighting (IPCW) to account for missing data due to dropout in both studies (37). This method assigns weights to individuals with complete follow-up data corresponding to the inverse of their estimated probability of having complete data. The IPCW model was specified with regard to the probability of missing data due to study dropout and included the following covariates: cohort affiliation, age, sex, symptom duration, CRP, ESR, patient global assessment of disease, SJC28, and TJC28. The final outcome model was a logistic regression model combining the baseline balancing with inverse probability of treatment weights, with the IPCW accounting for missing data due to dropout.

RESULTS

Patients and baseline characteristics. A total of 189 patients from the ARCTIC trial and 330 patients from the NOR-VEAC study fulfilled the common eligibility criteria (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41232/abstract). After balancing the cohorts using inverse probability of treatment weights, the distributions of baseline covariates were similar with standardized mean differences of <10%, which is considered negligible (Table 1) (31). Fifty-three patients (16.1%) included from the NOR-VEAC study and 6 patients (3.2%) included from the ARCTIC trial were missing ≥1 covariates for calculation of the propensity score at baseline, and these patients were excluded from comparative analyses using inverse probability

Table 2. Methotrexate dosage among patients receiving methotrexate monotherapy from baseline to 24 months in the ARCTIC trial and the NOR-VEAC study*

	ARCTIC trial	NOR-VEAC study	*P*
Baseline	16.0 ± 2.8	15.5 ± 2.8	0.05
3 months	20.7 ± 3.0	17.8 ± 4.0	<0.001
6 months	21.4 ± 3.7	18.4 ± 4.5	<0.001
12 months	21.3 ± 3.7	18.4 ± 4.6	<0.001
24 months	20.8 ± 4.3	18.0 ± 4.9	<0.001

* Values are the mean ± SD mg/week. ARCTIC = Aiming for Remission in Rheumatoid Arthritis: a randomised trial examining the benefit of ultrasound in a Clinical Tight Control regimen; NOR-VEAC = Norwegian Very Early Arthritis Clinic.

of treatment weights. No substantial differences in baseline characteristics or follow-up data were observed when comparing patients with complete data and those without complete data for calculation of the propensity score at baseline. The median classification score in patients who met the 2010 ACR/EULAR classification criteria for RA was similar in the 2 cohorts (median 7 [interquartile range 7–8] in ARCTIC and 7 [interquartile range 6–9] in NOR-VEAC; $P = 0.31$). Of the original 429 patients included in the NOR-VEAC study who were clinically diagnosed as having RA, 46 patients (10.7%) did not fulfill the 2010 ACR/EULAR classification criteria for RA and were excluded from the present study. Compared to patients who met the criteria, a significantly greater number of excluded patients were seronegative (43.5% versus 19.0%; $P < 0.001$), and mean disease activity was lower in both seropositive and seronegative patients (see Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41232/abstract).

Drug therapy and adverse events. Patients in both cohorts started MTX monotherapy, at a mean dosage of 16.0 mg/week in the ARCTIC trial and 15.5 mg/week in the NOR-VEAC study (Table 2). During follow-up, more patients in the NOR-VEAC study continued receiving the initial MTX monotherapy, while more patients in the ARCTIC trial switched to synthetic DMARD triple therapy (Figure 1). Therapy was escalated to a biologic DMARD regimen in a similar proportion of patients in the 2 cohorts (6.5% in the ARCTIC trial versus 6.0% in the NOR-VEAC study at 6 months, 17.1% versus 13.6% at 12 months, and 25.6% versus 25.4% at 24 months) (Figure 1).

During follow-up, mean dosages of MTX were higher in the ARCTIC trial than in the NOR-VEAC study (Table 2), which was mainly a result of the dosage of MTX being escalated to >20 mg/week in more patients in the ARCTIC trial (Figure 1). At baseline, more patients in the ARCTIC trial than in the NOR-VEAC study started co-medication with oral prednisolone (93.1% versus 56.7%; Table 3). At follow-up visits during the first year, more patients in the NOR-VEAC study were treated with prednisolone, while a similar proportion of patients in the 2 studies were treated with prednisolone at 24 months (Table 3). The mean ± SD dosage of prednisolone was higher in the ARCTIC trial than in the NOR-VEAC study at baseline (13.6 ± 3.4 mg versus 11.8 ± 4.3 mg; $P < 0.001$), but similar during follow-up.

In the ARCTIC trial, 529 treatment-emergent adverse events were observed compared to 379 in the NOR-VEAC study; however, a similar proportion of patients in the 2 cohorts switched treatment due to adverse events (see Supplementary Table 4, available on the *Arthritis & Rheumatology* web site at

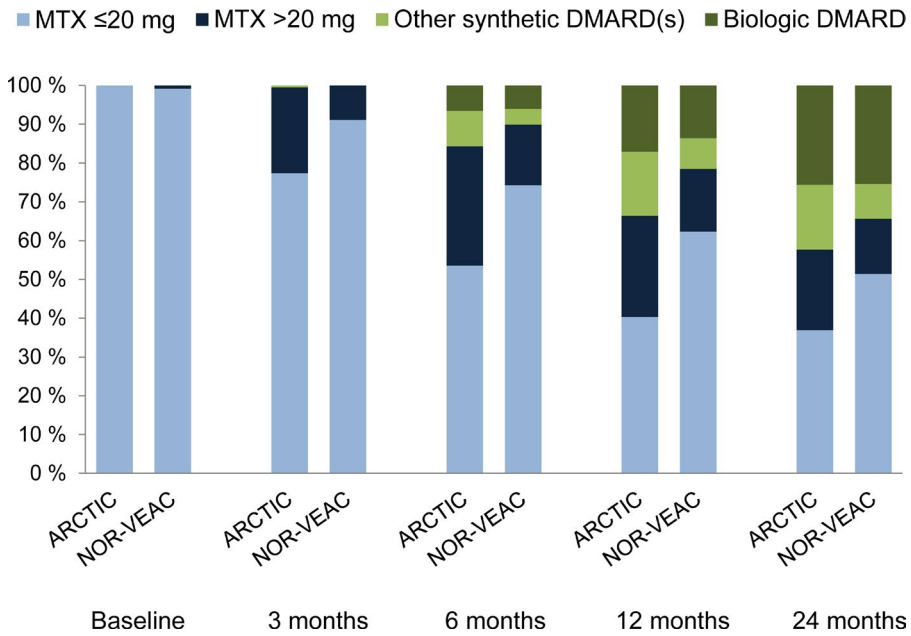

Figure 1. Percentage of patients receiving methotrexate (MTX) ≤20 mg/week, MTX >20 mg/week, other synthetic disease-modifying antirheumatic drugs (DMARDs), and biologic DMARDs at baseline and during follow-up in the Aiming for Remission in Rheumatoid Arthritis: a randomised trial examining the benefit of ultrasound in a Clinical Tight Control regimen (ARCTIC) trial versus the Norwegian Very Early Arthritis Clinic (NOR-VEAC) study.

Table 3. Co-medication with prednisolone from baseline to 24 months in the ARCTIC trial and the NOR-VEAC study*

	ARCTIC trial	NOR-VEAC study	*P*
Baseline	93.1	56.7	<0.001
3 months	17.4	38.2	<0.001
6 months	11.9	30.5	<0.001
12 months	12.9	25.4	0.001
24 months	11.8	13.2	0.7

* Values are the percent of patients. ARCTIC = Aiming for Remission in Rheumatoid Arthritis: a randomised trial examining the benefit of ultrasound in a Clinical Tight Control regimen; NOR-VEAC = Norwegian Very Early Arthritis Clinic.

http://onlinelibrary.wiley.com/doi/10.1002/art.41232/abstract). Of the 189 patients included in the ARCTIC trial, 5 patients experienced a serious adverse event, and of the 330 patients included in the NOR-VEAC study, 2 patients experienced a serious adverse event (Supplementary Table 4, http://onlinelibrary.wiley.com/doi/10.1002/art.41232/abstract).

Visit frequency during follow-up. The median number of follow-up visits in the ARCTIC trial corresponded to the 13 protocoled study visits over 2 years of follow-up. In the NOR-VEAC study, a median of 8 visits per patients was observed during 2 years of follow-up. The median time between visits during the first 12 months was 1.5 months (interquartile range 1.3–1.5) in the ARCTIC trial and 2.4 months (interquartile range 1.7–3.0) in the NOR-VEAC study. During the second year of follow-up, the median time between visits was 3.0 months (interquartile range 2.4–3.0) in the ARCTIC trial and 4.0 months (interquartile range 4.0–6.0) in the NOR-VEAC study.

Achievement of study-specific remission targets and ACR/EULAR Boolean remission. In the ARCTIC trial, the study-specific target of a DAS of <1.6 plus 0 swollen joints on a 44-joint count had been achieved in 37.4% of patients at 3 months, increasing to 53.5% of patients at 6 months, 69.8% of patients at 12 months, and 66.3% of patients at 24 months (Table 4). In the NOR-VEAC study, the less stringent target of DAS28 remission was achieved in 45.5% of patients at 3 months, 50.9% of patients at 6 months, 61.0% of patients at 12 months, and 65.1% of patients at 24 months (Table 4).

When comparing the observed achievement of ACR/EULAR Boolean remission in the 2 cohorts during follow-up, the remission rates were considerably higher in the ARCTIC trial (Table 4). Also, after balancing the 2 cohorts at baseline using propensity score weights and accounting for missing data with a combination of multiple imputation by chained equations and IPCW, the odds of reaching ACR/EULAR Boolean remission were significantly higher in the ARCTIC trial than in the NOR-VEAC study at 3, 12, and 24 months (Table 5).

At all follow-up visits, a majority of patients in both cohorts reached CDAI remission or low disease activity (see Supplementary Table 5, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41232/abstract). Remission according to the CDAI was achieved in more patients in the ARCTIC trial than in the NOR-VEAC study (37.9% versus 26.0% at 3 months, and increasing to 62.5% versus 44.0% at 24 months), while more patients in the NOR-VEAC study than in the ARCTIC trial had moderate or high disease activity (28.6% versus 24.8% at 3 months, and decreasing to 16.4% versus 7.9% at 12 months and 16.6% versus 12.5% at 24 months).

DISCUSSION

In this study, we compared achievement of remission in 2 early RA cohorts, examining whether a tight control TTT strategy targeting DAS remission plus 0 swollen joints on a 44-joint count in an RCT setting (the ARCTIC trial) led to superior disease activity outcomes compared to a TTT approach targeting DAS28 remission in an observational setting (the NOR-VEAC study). We found

Table 4. Percentage of patients in whom study-specific remission targets and ACR/EULAR Boolean remission were achieved during the follow-up period

	Study-specific remission target*		ACR/EULAR Boolean remission†	
	ARCTIC trial (n = 189)	NOR-VEAC study (n = 330)	ARCTIC trial (n = 183)	NOR-VEAC study (n = 277)
3 months	37.4	45.5	28.0	19.4
6 months	53.5	50.9	32.4	25.7
12 months	69.8	61.0	45.4	30.1
24 months	66.3	65.1	51.5	34.7

* The study-specific remission targets were a Disease Activity Score of <1.6 and 0 swollen joints on a 44-joint count in the Aiming for Remission in Rheumatoid Arthritis: a randomised trial examining the benefit of ultrasound in a Clinical Tight Control regimen (ARCTIC) trial and a Disease Activity Score in 28 joints of <2.6 in the Norwegian Very Early Arthritis Clinic (NOR-VEAC) study.
† American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Boolean remission was assessed in patients with recorded data for calculation of propensity scores at baseline and was defined as a C-reactive protein level of ≤1 mg/dl, a swollen joint count in 28 joints of ≤1, a tender joint count in 28 joints of ≤1, and patient global assessment of ≤1 on a 0–10 scale.

Table 5. Odds of achieving ACR/EULAR Boolean remission in the ARCTIC trial versus the NOR-VEAC observational study during follow-up*

Study visit	OR (95% CI)†	*P*‡
3 months	1.73 (1.03–2.89)	0.04
6 months	1.44 (0.88–2.38)	0.15
12 months	1.97 (1.21–3.20)	0.01
24 months	1.82 (1.05–3.16)	0.03

* The 2 cohorts were balanced on baseline covariates using inverse probability of treatment weights using the propensity score. Multiple imputation by chained equations was used to impute missing variables at existing visits in the Norwegian Very Early Arthritis Clinic (NOR-VEAC) study. ARCTIC = Aiming for Remission in Rheumatoid Arthritis: a randomised trial examining the benefit of ultrasound in a Clinical Tight Control regimen; OR = odds ratio; 95% CI = 95% confidence interval.
† American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Boolean remission was assessed in patients with recorded data for calculation of propensity scores at baseline and was defined as a C-reactive protein level of ≤1 mg/dl, a swollen joint count in 28 joints of ≤1, a tender joint count in 28 joints of ≤1, and patient global assessment of ≤1 on a 0–10 scale.
‡ *P* values were obtained using logistic regression with inverse probability of censoring weights to account for imbalanced missing data.

that more than half of the patients in each cohort had reached the study-specific remission targets at 6 months, and this number increased to more than 60% in each cohort at 12 and 24 months. However, ACR/EULAR Boolean remission was achieved in significantly more patients in the ARCTIC trial than in the NOR-VEAC study at 12 and 24 months, suggesting that tight control and targeting a more stringent definition of remission improves the disease activity outcomes of a TTT strategy.

The results demonstrate that a TTT approach is feasible in clinical practice and may lead to achievement of remission in a majority of patients. The proportion of patients reaching the treatment target of DAS28 remission in the NOR-VEAC observational study was similar to achievement of DAS28 remission in the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort (38). Further, achievement of remission according to both the DAS28 and ACR/EULAR Boolean criteria in the NOR-VEAC study during follow-up was more prevalent than previously described in conventional care cohorts (12,39,40). In both the ARCTIC trial and NOR-VEAC study, >80% of patients had reached remission or low disease activity according to the CDAI at 12 and 24 months, confirming the successful results of applying a TTT strategy in both an RCT setting and in clinical practice.

Different factors may explain why ACR/EULAR Boolean remission was achieved in more patients in the ARCTIC trial than in the NOR-VEAC study during follow-up. Therapy was escalated by increasing the dosage of MTX or by switching to synthetic DMARD triple therapy in more patients in the ARCTIC trial than in the NOR-VEAC study, which may have contributed to a lower degree of inflammation (41). Targeting a more stringent definition of remission in the ARCTIC trial is likely to have influenced therapy decisions during follow-up, leading to more therapy escalations. Furthermore, using a 44-joint count in the ARCTIC trial may have detected disease activity in joints not included in the DAS28 score used in the NOR-VEAC study (42), leading to better overall disease control in the ARCTIC trial. Another explanation may be that more frequent study visits in the ARCTIC trial led to earlier therapy escalations as a result of tight monitoring of disease activity, contributing to earlier disease control in the ARCTIC trial than in the NOR-VEAC study. Previous studies have suggested that the level of disease activity improvement during the first few months of therapy predicts subsequent disease activity levels (43–45). More frequent study visits in the ARCTIC trial may also have positively influenced patients' adherence to drug therapy by providing more opportunities for dialog between patient and provider about side effects, disease activity level, and the importance of reaching the desired target (46).

Considerably more treatment-emergent adverse events were recorded in the ARCTIC trial compared to the NOR-VEAC study, including more serious adverse events. This could suggest that the more aggressive treatment strategy leading to favorable disease activity outcomes in the ARCTIC trial also may increase the risk of harm to the patients. However, it is likely that frequent visits and close monitoring in the ARCTIC trial led to better recording of adverse events than in the NOR-VEAC study, which makes clear-cut conclusions challenging.

Limited data exist on comparing the outcomes of aiming for different definitions of remission in a TTT strategy. One previous study assessed 5-year outcomes when aiming for DAS remission compared to DAS low disease activity in 2 different early RA RCT cohorts (47). Targeting remission or targeting low disease activity led to similar functional and radiographic outcomes over time. However, similar to the present study, remission was achieved in a higher proportion of patients in the cohort aiming for the more stringent target (DAS remission). Another study compared routine care with TTT strategies aiming for either DAS28 remission or a target of no swollen joints in patients with established RA (19). The investigators found no significant differences in disease activity outcomes between the 2 TTT strategies during 18 months of follow-up.

Strengths of this study include the ability to compare patients across 2 Norwegian cohorts of DMARD-naive patients with early RA followed up during similar periods of time (2010–2013 and 2010–2016). The treatment algorithm in the ARCTIC trial was similar to the EULAR recommendations (26,27) that guided therapy in the NOR-VEAC study, enabling comparison of outcomes of TTT strategies with different targets and disease-monitoring approaches.

Methodologic challenges arising from the comparison of outcomes in patients from 2 different cohorts were addressed by applying common eligibility criteria and using propensity score weighting on baseline covariates, which enabled comparison of different strategies in similar patients. Further, we used a combi-

nation of methods to adjust for differences in follow-up patterns, with more frequent visits in the ARCTIC trial and more missing data in the NOR-VEAC study. The present study highlights the challenges of analyzing observational data, but also demonstrates how state-of-the-art statistical methods, considering subtle forms of selection bias, facilitate comparison of RCT data with observational data.

The main limitation of this study was comparing outcomes of treatment strategies in 2 different cohorts with different study designs, which presented a risk for biased estimates. In the ARCTIC trial, patients and rheumatologists agreed to adhere to the treatment plan and visits specified in the protocol. During the conduct of the study, investigators entered clinical and ultrasound assessments into a data program that provided a recommendation of whether or not to escalate therapy (20). This is likely to have positively influenced adherence to the TTT strategy (48,49). In the NOR-VEAC study, current EULAR recommendations guided therapy decisions, which might have given the individual preferences of patients and provider, as well as available time and resources at the study centers, a larger influence over treatment decisions and follow-up (48,49). If commitment to the TTT strategy by patients and rheumatologists was better in the ARCTIC trial than in the NOR-VEAC study, this may in part explain the favorable disease activity outcomes in the ARCTIC trial.

Another limitation of the present study was that the eligibility criteria applied may limit the generalizability of results to a broader population. In both the ARCTIC trial and the NOR-VEAC study, inclusion was restricted to patients age 18–75 years. Excluding older patients may have led to less comorbidity, fewer adverse events, and better treatment response (50). Furthermore, patients in the NOR-VEAC study who were excluded from the present study due to not fulfilling the 2010 ACR/EULAR classification criteria for RA had lower disease activity than patients who fulfilled the criteria, and more were seronegative. These patients, likely to be observed in clinical practice, may have required less intensive therapy to reach the treatment target.

Finally, comparison of radiographic data may have contributed to a more clear-cut clinical conclusion and the lack of such data in the NOR-VEAC study represented another limitation of this study.

In conclusion, we found that TTT implemented in an observational cohort resulted in high remission rates according to the study-specific target, similar to a TTT clinical trial. This confirms that TTT is feasible in clinical practice and should encourage wider implementation of TTT principles. However, significantly more patients in the ARCTIC trial reached ACR/EULAR Boolean remission during follow-up, indicating that targeting a more stringent definition of remission and implementing more frequent visits provide further potential for favorable outcomes of a TTT strategy. Both the ARCTIC trial and the NOR-VEAC study employed protocols for TTT, demonstrating the value of algorithms to improve rheumatologic care.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual contact, and all authors approved the final version to be published. Dr. Norvang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Norvang, Brinkmann, Yoshida, Lillegraven, Aga, Sexton, Tedeschi, Uhlig, Kvien, Mjaavatten, Solomon, Haavardsholm.

Acquisition of data. Brinkmann, Aga, Norli, Uhlig, Mjaavatten, Haavardsholm.

Analysis and interpretation of data. Norvang, Yoshida, Lillegraven, Aga, Sexton, Tedeschi, Lyo, Uhlig, Kvien, Mjaavatten, Solomon, Haavardsholm.

REFERENCES

1. Smolen JS, Breedveld FC, Burmester GR, Bykerk V, Dougados M, Emery P, 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. Burmester GR, Pope JE. Novel treatment strategies in rheumatoid arthritis. Lancet 2017;389:2338–48.
3. Stoffer MA, Schoels MM, Smolen JS, Aletaha D, Breedveld FC, Burmester G, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update [review]. Ann Rheum Dis 2016;75:16–22.
4. Schoels M, Knevel R, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas DT, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. Ann Rheum Dis 2010;69:638–43.
5. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2016;68:1–26.
6. Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960–77.
7. Sepriano A, Ramiro S, FitzGerald O, Østergaard M, Homik J, van der Heijde D, et al. Adherence to treat-to-target management in rheumatoid arthritis and associated factors: data from the international RA BIODAM cohort. J Rheumatol 2019. https://doi.org/10.3899/jrheum.190303. E-pub ahead of print.
8. Tymms K, Zochling J, Scott J, Bird P, Burnet S, de Jager J, et al. Barriers to optimal disease control for rheumatoid arthritis patients with moderate and high disease activity. Arthritis Care Res (Hoboken) 2014;66:190–6.
9. Zak A, Corrigan C, Yu Z, Bitton A, Fraenkel L, Harrold L, et al. Barriers to treatment adjustment within a treat to target strategy in rheumatoid arthritis: a secondary analysis of the TRACTION trial. Rheumatology (Oxford) 2018;57:1933–7.
10. Reed GW, Collier DH, Koenig AS, Saunders KC, Pappas DA, Litman HJ, et al. Clinical and demographic factors associated with change and maintenance of disease severity in a large registry of patients with rheumatoid arthritis. Arthritis Res Ther 2017;19:81.
11. Yun H, Chen L, Xie F, Patel H, Boytsov N, Zhang X, et al. Do patients with moderate or high disease activity escalate RA therapy accord-

ing to treat-to-target principles? Results from the Rheumatology Informatics System for Effectiveness Registry of the American College of Rheumatology. Arthritis Care Res (Hoboken) 2020;72:166–75.

12. Einarsson JT, Willim M, Ernestam S, Saxne T, Geborek P, Kapetanovic MC. Prevalence of sustained remission in rheumatoid arthritis: impact of criteria sets and disease duration, a nationwide study in Sweden. Rheumatology (Oxford) 2019;58:227–36.
13. Klarenbeek NB, Koevoets R, van der Heijde DM, Gerards AH, Ten Wolde S, Kerstens PJ, et al. Association with joint damage and physical functioning of nine composite indices and the 2011 ACR/EULAR remission criteria in rheumatoid arthritis. Ann Rheum Dis 2011;70:1815–21.
14. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63:573–86.
15. Sakellariou G, Scirè CA, Verstappen SM, Montecucco C, Caporali R. In patients with early rheumatoid arthritis, the new ACR/EULAR definition of remission identifies patients with persistent absence of functional disability and suppression of ultrasonographic synovitis. Ann Rheum Dis 2013;72:245–9.
16. Ruyssen-Witrand A, Guernec G, Nigon D, Tobon G, Jamard B, Rat AC, et al. Aiming for SDAI remission versus low disease activity at 1 year after inclusion in ESPOIR cohort is associated with better 3-year structural outcomes. Ann Rheum Dis 2015;74:1676–83.
17. Smolen JS, Han C, van der Heijde DM, Emery P, Bathon JM, Keystone E, et al. Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. Ann Rheum Dis 2009;68:823–7.
18. Combe B, Logeart I, Belkacemi MC, Dadoun S, Schaeverbeke T, Daurès JP, et al. Comparison of the long-term outcome for patients with rheumatoid arthritis with persistent moderate disease activity or disease remission during the first year after diagnosis: data from the ESPOIR cohort. Ann Rheum Dis 2015;74:724–9.
19. Pope JE, Haraoui B, Rampakakis E, Psaradellis E, Thorne C, Sampalis JS. Treating to a target in established active rheumatoid arthritis patients receiving a tumor necrosis factor inhibitor: results from a real-world cluster-randomized adalimumab trial. Arthritis Care Res (Hoboken) 2013;65:1401–9.
20. Haavardsholm EA, Aga AB, Olsen IC, Lillegraven S, Hammer HB, Uhlig T, et al. Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial. BMJ 2016;354:i4205.
21. Brinkmann GH, Norvang V, Norli ES, Grøvle L, Haugen AJ, Lexberg AS, et al. Treat to target strategy in early rheumatoid arthritis versus routine care: a comparative clinical practice study. Semin Arthritis Rheum 2019;48:808–14.
22. Van der Heijde DM, van 't Hof M, van Riel PL, van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. J Rheumatol 1993;20:579–81.
23. Van Riel PL, van Gestel AM. Clinical outcome measures in rheumatoid arthritis. Ann Rheum Dis 2000;59 Suppl 1:i28–31.
24. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569–81.
25. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight–joint counts: development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.
26. Smolen JS, Landewé R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010;69:964–75.
27. Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492–509.
28. Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010;69:631–7.
29. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, 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.
30. Aletaha D, Ward MM, Machold KP, Nell VP, Stamm T, Smolen JS. Remission and active disease in rheumatoid arthritis: defining criteria for disease activity states. Arthritis Rheum 2005;52:2625–36.
31. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015;34:3661–79.
32. Rosenbaum PR, Rubin DB. The central role of propensity score in observational studies for causal effects. Biometrika 1983;70:41–55.
33. Rubin DB. Inference and missing data. Biometrika 1976;63:581–92.
34. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Stat Med 2011;30:377–99.
35. Van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. Stat Methods Med Res 2007;16:219–42.
36. Robins JM, Rotnitzky A, Zhao LP. Analyses of semiparametric regression models for repeated outcomes in the presence of missing data. J Am Stat Assoc 1995;90:106–21.
37. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. Stat Methods Med Res 2013;22:278–95.
38. Vermeer M, Kuper HH, Moens HJ, Drossaers-Bakker KW, van der Bijl AE, van Riel PL, et al. Sustained beneficial effects of a protocolized treat-to-target strategy in very early rheumatoid arthritis: three-year results of the Dutch Rheumatoid Arthritis Monitoring remission induction cohort. Arthritis Care Res (Hoboken) 2013;65:1219–26.
39. Britsemmer K, van Schaardenburg D, Boers M, de Cock D, Verschueren P, Radner H, et al. Prevalence and validity of ACR/EULAR remission in four European early rheumatoid arthritis cohorts. Clin Exp Rheumatol 2018;36:362–70.
40. Conigliaro P, Chimenti MS, Triggianese P, Ballanti E, Sunzini F, Duca I, et al. Remission and low disease activity in a cohort of real-life patients with rheumatoid arthritis treated with first-line antitumour necrosis factor. J Int Med Res 2016;44:90–4.
41. Visser K, van der Heijde D. Optimal dosage and route of administration of methotrexate in rheumatoid arthritis: a systematic review of the literature. Ann Rheum Dis 2009;68:1094–9.
42. Landewé R, van der Heijde D, van der Linden S, Boers M. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. Ann Rheum Dis 2006;65:637–41.
43. Aletaha D, Funovits J, Keystone EC, Smolen JS. Disease activity early in the course of treatment predicts response to therapy after one year in rheumatoid arthritis patients. Arthritis Rheum 2007;56:3226–35.

44. Schipper LG, Fransen J, den Broeder AA, van Riel PL. Time to achieve remission determines time to be in remission. Arthritis Res Ther 2010;12:R97.
45. Kuriya B, Xiong J, Boire G, Haraoui B, Hitchon C, Pope J, et al. Earlier time to remission predicts sustained clinical remission in early rheumatoid arthritis: results from the Canadian Early Arthritis Cohort (CATCH). J Rheumatol 2014;41:2161–6.
46. Hope HF, Hyrich KL, Anderson J, Bluett J, Sergeant JC, Barton A, et al. The predictors of and reasons for non-adherence in an observational cohort of patients with rheumatoid arthritis commencing methotrexate. Rheumatology (Oxford) 2020;59:213–23.
47. Akdemir G, Markusse IM, Bergstra SA, Goekoop RJ, Molenaar ET, van Groenendael J, et al. Comparison between low disease activity or DAS remission as treatment target in patients with early active rheumatoid arthritis. RMD Open 2018;4:e000649.
48. Weiss NS. Generalizing from the results of randomized studies of treatment: can non-randomized studies be of help? Eur J Epidemiol 2019;34:715–8.
49. Beaulieu-Jones BK, Finlayson SG, Yuan W, Altman RB, Kohane IS, Prasad V, et al. Examining the use of real-world evidence in the regulatory process. Clin Pharmacol Ther 2020;107:843–52.
50. Soubrier M, Tatar Z, Couderc M, Mathieu S, Dubost JJ. Rheumatoid arthritis in the elderly in the era of tight control. Drugs Aging 2013;30:863–9.

APPENDIX A: THE ARCTIC TRIAL GROUP AND THE NOR-VEAC STUDY GROUP INVESTIGATORS

The ARCTIC trial group investigators are as follows: Hallvard Fremstad, Tor Magne Madland, Åse Stavland Lexberg, Hilde Haukeland, Erik Rødevand, Christian Høili, Hilde Stray, Anne Noraas Bendvold, Inger Johanne Widding-Hansen, Gunnstein Bakland.

The NOR-VEAC study group investigators are as follows: Åse Stavland Lexberg, Cathrine Thunem, Inger Johanne Widding-Hansen, Heidi Kverneggen Øvreås.