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Is treat-to-target really working in rheumatoid arthritis? A longitudinal analysis of a cohort of patients treated in daily practice (RA BIODAM)

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Abstract

Objectives: To investigate whether following a treat-to-target (T2T)-strategy in daily clinical practice leads to more patients with rheumatoid arthritis (RA) meeting the remission target.

Methods: RA patients from 10 countries starting/changing conventional synthetic or biologic disease-modifying anti-rheumatic drugs were assessed for disease activity every 3 months for 2 years (RA BIODAM cohort). Per visit was decided whether a patient was treated according to a T2T-strategy with DAS44 remission (DAS44<1.6) as the target. Sustained T2T was defined as T2T followed in 2 consecutive visits. The main outcome was the achievement of DAS44 remission at the subsequent 3-month visit. Other outcomes were remission according to DAS28-ESR, CDAI, SDAI and ACR/EULAR Boolean definitions. The association between T2T and remission was tested in generalized estimating equations models.

Results: In total 4,356 visits of 571 patients [mean (SD) age: 56 (13) years, 78% female] were included. Appropriate application of T2T was found in 59% of the visits. T2T (vs no T2T) did not yield a higher likelihood of DAS44 remission 3 months later [OR (95%CI): 1.03 (0.92;1.16)], but sustained T2T resulted in an increased likelihood of achieving DAS44 remission [OR: 1.19 (1.03;1.39)]. Similar results were seen with DAS28-ESR remission. For more stringent definitions (CDAI, SDAI and ACR/EULAR Boolean remission), T2T was consistently positively associated with remission (OR range: 1.16-1.29), and sustained T2T had a more pronounced effect on remission (OR range: 1.49-1.52).

Conclusion: In daily clinical practice, the correct application of a T2T-strategy (especially sustained T2T) in patients with RA leads to higher rates of remission.

Key messages (up to 5 bullet points):

What is already known about this subject?

- Randomized controlled trials have demonstrated the efficacy of treat-to-target approaches in rheumatoid arthritis. Real life data from cohorts are still needed to support the widespread implementation of T2T in clinical practice.

What does this study add?

- In daily clinical practice, the correct application of a T2T-strategy in patients with RA leads to higher rates of remission as compared to not following it.
- Not only in early RA, but also in established RA, following a T2T-strategy leads to higher remission rates.

How might this impact on clinical practice or future developments?

- Rheumatologists should be encouraged to follow a T2T-strategy to contribute to the achievement of higher rates of remission for their patients.

Introduction

Early diagnosis, prompt commencement of disease modifying antirheumatic drug (DMARD) treatment and applying treat-to-target (T2T) strategies are now engrained in rheumatoid arthritis (RA) treatment paradigms. These approaches have substantially improved the outcomes of patients with RA.[1] Remission has been defined and agreed upon as the optimal target when managing a patient with RA.[2,3] Reaching the state of remission is associated with reduced radiographic progression and improved functional ability.[4]

Thoroughly monitoring disease activity, adjusting treatment according to a fixed protocol and aiming at a predefined treatment goal, the so-called T2T-strategy, has advantages over usual care.[5,6] Several strategy studies provide the basis of this evidence, namely the TICORA (Tight Control of RA study)[7] and CAMERA (Computer Assisted Management in Early RA)[8] studies. Subsequently, several strategy studies have incorporated a T2T-strategy in their treatment algorithm in the formal comparison of specific therapies, such as was done in the BeSt (Behandel Strategiëen) study.[9] However, such evidence was gathered in the setting of randomized controlled trials (RCTs), with strict inclusion and exclusion criteria, following strict protocols and all particularities of RCTs. These studies provide the best evidence for the efficacy of T2T as an intervention, but to some extent compromise the generalizability of the findings, when one wants to consider applying them more broadly.

Having formally demonstrated the efficacy of T2T in RCTs, it is important to assess whether this strategy also improves outcomes in unselected patients from daily clinical practice. The first cohort studies focused on patients with very early disease and confirmed that following a standardized intensive treatment led to improved achievement of remission.[10] Subsequently, some cohort studies have shown that tight-control treatment leads to more rapid remission and higher remission achievement after 1 or 2 years than usual care.[11,12] Nevertheless, the conclusions from these 2 studies were based on an indirect comparison between 2 different cohorts (one with T2T applied and another with usual care), with different patient characteristics, and focused on the remission achievement at 1 or 2 years in the 2 cohorts. Such a comparison should ideally be made within the same cohort of patients, wherein some patients receive a T2T-strategy while others receive usual care. Real life data from cohorts without strict protocol specifications regarding choice of treatment are still needed to support the widespread implementation of T2T in clinical practice. Furthermore, previous studies have focused on the achievement of remission at a given time point, e.g. 1 or 2 years, ignoring whether or not the remission outcome was achieved in each of the visits throughout the follow-up (e.g. 3 monthly visits, per T2T recommendations). A true longitudinal analysis taking all observations over time into account, both in terms of following T2T or not, and

achieving remission or not, reflecting daily clinically practice, has not yet been conducted. Additionally, T2T has not yet been investigated in patients with established RA.

The aim of the present study was to investigate whether following a T2T-strategy leads to more patients with RA meeting the treatment target (remission) in daily clinical practice.

Methods

Study population

Patients from RA BIODAM (BIOmarkers of joint DAMage), which has been previously described, were included.[13] In brief, RA BIODAM is a 2-year multi-national prospective observational study, including patients with a clinical diagnosis of RA and also fulfilling the 2010 RA Classification Criteria,[14] recruited in daily practice from 10 countries from October 2011 to April 2015. To be eligible patients presented with active disease (44-joint disease activity score, DAS44>2.4)[15] and were to be started on or changing DMARD treatment, including conventional synthetic DMARDs (csDMARDs) and a first tumor necrosis factor inhibitor (TNFi); patients who had prior biologic (b)DMARD experience were excluded. All patients were included in this analysis. The database used for this analysis was locked in April 2017. The study fulfilled Good Clinical Practice Guidelines, received ethical approval from the local ethics committees, and all patients provided informed consent.

Remission

Remission was the outcome of interest. According to the study protocol, patients were monitored every 3 months using DAS44 calculated with the erythrocyte sedimentation rate (ESR).[15] DAS44 remission, i.e. DAS44<1.6[16] was therefore chosen as the main outcome for this analysis. Alternative definitions of remission were also used, namely the 28-joint disease activity score[17] (DAS28-ESR) remission (i.e. DAS28-ESR<2.6),[18] the Clinical Disease Activity Index (CDAI) remission (i.e. CDAI≤2.8),[19] the Simplified Disease Activity Index (SDAI) remission (SDAI≤3.3),[20] and the American College of Rheumatology / European League Against Rheumatism (ACR/EULAR) Boolean remission (i.e. tender joint count (TJC)≤1, swollen joint count (SJC)≤1, C-reactive protein (CRP)≤1mg/dL and patient global assessment (PGA) (0-10)≤1).[2] All definitions of remission were binary (yes/no).

Treat-to-target

Participating rheumatologists were required by protocol to follow a T2T-strategy with DAS44 remission (DAS44<1.6) as benchmark. In order to define whether a T2T-strategy was appropriately followed or not, every visit was checked according to pre-defined criteria. T2T was considered appropriate: i) if a patient had already a disease activity score below the target (DAS<1.6) and treatment was not intensified; or ii) if treatment was intensified upon a DAS≥1.6. Treatment intensification was defined as increasing dosage or adding a drug from the following categories: csDMARDs, bDMARDs or corticosteroids. T2T was considered incorrectly applied if: i) the target was met and treatment was nevertheless intensified; or ii) the target was not met and treatment was not intensified.

Additional definitions for T2T were also considered for sensitivity analyses: i) T2T without corticosteroids, i.e. without considering corticosteroids as a treatment intensification; ii) T2T less strict, i.e. considering T2T as adequate as long as the target, DAS44 remission, is met, regardless of whether treatment is nevertheless intensified or not; iii) T2T-low disease activity (T2T-LDA) using LDA (i.e. DAS<2.4)[21] instead of remission as the benchmark.

Furthermore, 'sustained T2T' strategy was defined as following T2T in at least 2 consecutive visits.

Other relevant clinical information

Age, gender, disease duration, rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) status (positive/negative) and being DMARD-naïve (yes vs no), all collected at baseline, were considered in this analysis as potential effect modifiers or confounders of the relationship of interest. Country of residence was also considered as a potential confounder.

Statistical analysis

The relationship between following T2T at a given visit and meeting the target of remission at the subsequent visit 3 months later was investigated using time-lagged generalized estimating equations (GEE) models. GEE is a suitable technique to make use of all available observations from each patient while adjusting for inherent within-subject correlations of the repeated measurements. Models were time-lagged to allow investigation of the effect of the main predictor of interest (i.e. following T2T) on the outcome (i.e. remission) with a lag of 3 months; in other words, with the outcome occurring 3 months later. The same analyses were conducted to investigate the effect of sustained T2T on meeting the target of remission. The 'exchangeable' working correlation structure, demonstrating the best fit to the data, was used.

As treatment intensification has a central role in T2T, we sought to investigate the extent to which the components of the disease activity scores contributed to it. We

therefore investigated the effect of TJC>1, SJC>1, PGA>1 and CRP>1mg/dL on treatment intensification (yes/no). This analysis was also conducted with GEE, including all above-mentioned disease activity components in one multivariable model.
For each model, interactions between the T2T variable and age, gender, disease duration and RF/ACP positivity were tested, and if significant ($p<0.15$) and clinically relevant the model was fitted in each subgroup. If these proved to be not relevant, final models were adjusted for potential confounders selected *a priori*: age, gender, disease duration and country of residence. Stata SE version 12 was used.

Results

In total, 571 patients were included with a mean age of 56 (SD 13) years, 78% females and a mean disease duration of 6.5 (8.0) years, 37% with a disease duration up to 2 years (Table 1). In total, 78% of the patients were RF and/or ACPA positive, and 48% were DMARD-naive at baseline (mean disease duration of 3.6 (5.6), 50% with ≤2-year disease duration). At the end of the baseline visit, almost 60% of the patients were on treatment with csDMARDs only, 35% of the patients on a TNFi with a csDMARD and only 6% on TNFi monotherapy. Almost half of the patients were on corticosteroids after the baseline visit.

T2T was appropriately applied in 59% of 4,356 visits. This included 31% of patient visits where DAS44 remission was met and treatment was not intensified, and 28% of visits where treatment was appropriately escalated. In 3% of visits (9% of those with treatment intensification), treatment intensification took place even though DAS44 remission was met (making a total of 31% of the visits with treatment intensification). In the remaining 38% of visits T2T was not being followed as there was no treatment intensification despite active disease (DAS44≥1.6) (Figure 1).

Throughout the 2-year follow-up period an increasing proportion of patients met remission definitions. At 3 months 24% of the patients were in DAS44 and DAS28-ESR remission, and 8% in ACR/EULAR Boolean remission. At 24 months 52% of the patients were in DAS44 remission, also 52% in DAS28-ESR remission and 27% in ACR/EULAR Boolean remission (Figure 2).

T2T on remission outcomes

Following a T2T-strategy, as compared to not following it, was not significantly associated with a DAS44 or DAS28-ESR remission 3 months later (odds ratio (95% confidence interval) 1.03 (0.92; 1.16) and 1.03 (0.91; 1.16), respectively), but was significantly associated with ACR/EULAR Boolean remission (OR 1.16 (1.01; 1.34)) and also with CDAI remission (OR 1.29 (1.12; 1.49)) and SDAI remission (OR 1.24 (1.08; 1.41)) (Table 2). Results of the sensitivity analyses were similar, except for a

slightly stronger association between T2T and remission outcomes for both 'T2T without corticosteroids' and 'T2T-REM less strict'. With T2T-LDA, with LDA as the benchmark, there was a significant association between T2T and all remission outcomes (OR between 1.3 and 1.4). None of the tested effect modifiers, namely age, gender, disease duration, seropositivity or DMARD naïve (vs not), modified the relationships of interest.

Sustained T2T on remission outcomes

Following a sustained T2T-strategy compared to not following it was associated with remission 3 months later according to all definitions, e.g. DAS44 remission OR 1.19 (1.03; 1.39) or ACR/EULAR Boolean remission (OR 1.49 (1.24;1.81)) (Table 3).

Relationship between disease activity components and treatment intensification

All disease activity components were significantly associated with treatment intensification, with SJC and TJC showing the strongest associations, also in a multivariable model including all the components: OR 'SJC>1' 3.42 (2.89; 4.05), OR 'TJC>1' 3.35 (2.72; 4.11), OR 'PGA>1' 2.14 (1.71; 2.68) and OR 'CRP>1' 2.00 (1.66; 2.42).

Discussion

In the present study we have shown that following a T2T-strategy, and particularly sustained T2T, in daily clinical practice leads to more patients with RA meeting the most stringent remission criteria over time. This is the first comprehensive analysis that considers all available visits of unselected patients who were followed by protocol for a period of 2 years. The results of the analysis provide direct evidence that following T2T, and particularly sustained T2T, immediately results in a higher likelihood of remission at the next visit, 3 months later (the longitudinal interpretation of a T2T-strategy). Moreover, we have for the first time shown that following T2T is also efficacious in patients with established RA, while previous studies focused on the effect of T2T in patients with early RA.

The strictly temporal relationship between following a T2T-strategy and meeting remission was statistically significant for almost all remission outcomes and for the different T2T definitions used. The exceptions were the DAS44 and DAS28-ESR remission definitions with an interval of 3 months only, while for sustained T2T the relationship with all remission outcomes was statistically significant. The explanation is rather technical: the independent variable (T2T with DAS44 as benchmark) and the outcome (i.e. DAS44 remission) include exactly the same disease activity score, which implies that the model becomes inherently auto-regressive. Such a scenario effectively removes the variability in the data necessary to demonstrate efficacy of an intervention. The other definitions of remission are slightly different from the

benchmark definition and allow more statistical separation. An alternative explanation is that DAS44 and DAS28-ESR definitions are more lenient in comparison to ACR/EULAR Boolean, CDAI, and SDAI remission and are more frequently met even if T2T is not applied.[2] Nevertheless, the signal that a T2T-strategy, and particularly sustained T2T-strategy, increases the likelihood of stringent remission is clear and consistent. Also, these findings became even more evident throughout the follow-up of this study. The proportion of patients achieving remission, regardless of its definition, increased substantially through follow-up (Figure 2). Even after 2 years, a plateau has not yet been reached, reassuring clinicians that if we measure disease activity and treat patients effectively over time, high remission rates can be achieved.

These findings come from a population of patients with an average of 6.5 years of disease duration. One may speculate that the effect of following T2T could be even better in early disease. In this study, we have not found any differences between patients DMARD naïve vs not and also according to disease duration, but a lack of statistical power cannot be excluded. Additionally, even patients who were DMARD naïve had a relatively long disease duration (average of 3.6 years), not being the most representative DMARD naïve patients.

If T2T is so clearly associated with clinical remission, as shown here and in the literature, [5,6] why, then, is a T2T-strategy not always followed in clinical practice? Even in this study, with a protocol requiring implementation of T2T, this strategy was 'only' followed in less than two thirds of the visits. Also within the RA BIODAM cohort, we have shown that, among other factors, the absence of objective signs of inflammation (e.g. swollen joints) implied a lower likelihood to follow T2T.[22] Also, in the 10-year follow-up of the BeSt trial, non-adherence to the protocol has been assigned to disagreement with how DAS reflects disease activity (felt to overestimate the real disease activity) and disagreement with the subsequently required step in the protocol.[23] Many clinicians find regularly measuring disease activity too time consuming endeavour and consider it an additional barrier to implementation of T2T.[24,25]

In order to launch new strategies or interventions in clinical practice, the formulation of recommendations, like the T2T recommendations,[27] does not suffice, and implementation should actively be promoted. Studies like ours may further corroborate the message that T2T leads to more stringent remission and may help implementation in clinical practice. Appropriate education may also help. The intervention of the TRACTION trial included one educational face-to-face meeting and monthly webinars on the principles and practical advice on implementation of T2T. A substantial improvement in the adherence to T2T was demonstrated with improvement of 46% in the arm following the training program compared to 14% in the control arm.[28] Still, rheumatologists may report compliance with recommendations but in practice do not always follow them.[29]

Some limitations of this study need to be considered. First, it is designed as an observational study reflecting daily clinical practice with unselected patients contrasting with the reality of RCTs from which most evidence on T2T originates to date. However, one may question how close to daily clinical practice the RA BIODAM cohort really is, with participation from only a few centers per country, several being tertiary referral centers, and with rheumatologists mandated to follow a strict T2T protocol. As in principle, rheumatologists were required to follow T2T per protocol, we have in this study in essence compared the visits in which the protocol was followed to others in which protocol was violated. One can therefore not exclude a bias intrinsic to this comparison. Additionally, detailed reasons for not following T2T have not been adequately registered precluding additional analysis of adherence to T2T versus taking the physician's reasoning into account. Moreover, only patients with active disease were included, and the average baseline disease activity was high. This may preclude the generalizability of the findings to patients with low disease activity, and not answer the question of whether following a T2T-strategy is beneficial in patients already in low disease activity, given the risks of overtreatment.[30,31] Lastly, when investigating the impact of following a T2T-strategy, one is not only analysing the impact of treatment intensification but implicitly one is evaluating visits in which patients are already in remission, which have accentuated the benefit of T2T. However, it was our aim to investigate the impact of following the T2T-strategy in its whole and not parts of it, as well as to take all disease activity measurements into account as the longitudinal technique chosen properly does. As a main strength, this is a multinational observational study, including unselected patients reflecting daily clinical practice, with the first truly longitudinal analysis addressing the impact of following a (sustained) T2T-strategy.

In conclusion, following a T2T-strategy, and especially sustained T2T, works in daily clinical practice and leads to more patients meeting the target, i.e. remission. Rheumatologists should be encouraged to follow a T2T-strategy to contribute to the achievement of higher rates of remission for their patients.

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All authors made contributions to conception and/or implementation of the study, were involved in reviewing and revising the manuscript, and gave final approval to the version to be published.

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Competing interests

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Patient and Public Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy

Table 1 - Baseline characteristics

	N = 571 Mean (SD) or n (%)
Age, years	55.7 (12.9)
Female gender	434 (76.0%)
Disease duration, years	6.5 (8.0)
Education, years	12.6 (3.8)
Number of comorbidities	1.2 (1.3)
Rheumatoid factor positivity	370 (68.0%)
Anti-CCP positivity	388 (69.3%)
RF and/or anti-CCP positivity	431 (77.7%)

DAS44 (0-10)	3.8 (1.0)
DAS28-ESR (0-10)	5.2 (1.2)
CDAI (0-76)	26.9 (11.6)
SDAI (0-86)	28.5 (12.4)
Patient global (0-10)	5.7 (2.3)
HAQ (0-3)	1.1 (0.7)
SJC (0-44)	8.4 (6.1)
TJC (0-53)	13.6 (9.1)
ESR (mm/h)	28.7 (22.2)
CRP (mg/dL)	1.5 (2.3)
Number of prior DMARDs	0.9 (1.1)
DMARD naïve	274 (48.0%)
Smoking status	
- **Never smoker**	282 (49.4%)
- **Current smoker**	161 (28.2%)
- **Ex-smoker**	128 (22.4%)
Treatment csDMARD/TNFi started at baseline	
- **Both**	196 (34.6%)
- **csDMARD only**	334 (58.9%)
- **TNFi only**	36 (6.3%)
- **None**	1 (0.2%)
Treatment with oral corticosteroids started at baseline	255 (45%)

Anti-CCP: anti-citrullinated protein; RF: rheumatoid factor; DAS44: 44-joint disease activity score; DAS28-ESR: 28-joint disease activity score (with erythrocyte sedimentation rate); CDAI: Clinical Disease Activity Index; SDAI: Simple Disease Activity Index; HAQ: health assessment questionnaire; SJC: swollen joint count; TJC: tender joint count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DMARD: disease modifying anti-rheumatic drug; csDMARD: conventional synthetic disease modifying anti-rheumatic drug; TNFi: tumor necrosis factor inhibitor

Figure 1 - Proportion of the visits (n = 4,356) in which treat-to-target strategy (with DAS44<1.6 as benchmark) is followed vs not and the details regarding the proportion of visits with target achievement and/or treatment intensification. Treatment intensification was defined as start or dosage increase of a conventional synthetic or biological disease modifying antirheumatic drug or of a corticosteroid.
DAS44: 44-joint disease activity score

Figure 2 – Proportion of achievement of the different remission outcomes throughout the 2-year follow-up. DAS44: 44-joint disease activity score; DAS28-ESR: 28-joint disease activity score; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; CDAI: Clinical Disease Activity Index; SDAI: Simple Disease Activity Index

Table 2 – Effect of following treat-to-target strategies on remission outcomes 3 months later*

	DAS44 remission (OR (95% CI))	DAS28-ESR remission (OR (95% CI))	ACR/EULAR Boolean remission (OR (95% CI))	CDAI remission (OR (95% CI))	SDAI remission (OR (95% CI))
T2T	1.03 (0.92; 1.16)	1.03 (0.91; 1.16)	**1.16 (1.01; 1.34)**	**1.29 (1.12; 1.49)**	**1.24 (1.08; 1.41)**
T2T without corticosteroids	1.07 (0.95; 1.20)	1.11 (0.98; 1.26)	**1.23 (1.06; 1.42)**	**1.37 (1.18; 1.59)**	**1.34 (1.17; 1.53)**
T2T-REM less strict	1.06 (0.94; 1.19)	1.07 (0.95; 1.21)	**1.32 (1.13; 1.53)**	**1.43 (1.22; 1.67)**	**1.34 (1.17; 1.54)**
T2T-LDA	**1.26 (1.10; 1.44)**	**1.36 (1.17; 1.56)**	**1.27 (1.09; 1.47)**	**1.39 (1.18; 1.64)**	**1.36 (1.17; 1.59)**

* All models adjusted for age, gender, disease duration and country. T2T was considered being followed: i) if a patient had already a disease activity score below the target (DAS<1.6; DAS<2.4 for LDA definition) and treatment was correctly not intensified; or ii) if treatment was intensified upon a DAS≥1.6 (or DAS ≥2.4 for LDA definition). T2T without corticosteroids: without considering corticosteroids in treatment intensification. T2T-REM less strict: considering T2T as adequate as long as the target, DAS44 remission, is met, regardless of whether treatment nevertheless intensified or not. T2T: treat-to-target; LDA: low disease activity; DAS44: 44-joint disease activity score; DAS28-ESR: 28-joint disease activity score; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; CDAI: Clinical Disease Activity Index; SDAI: Simple Disease Activity Index; OR: odds ratio; CI: confidence interval.

Table 3 - Effect of following a sustained treat-to-target strategy on remission outcomes 3 months later*

	DAS44 sustained remission (OR (95% CI))	DAS28-ESR sustained remission (OR (95% CI))	ACR/EULAR Boolean sustained remission (OR (95% CI))	CDAI sustained remission (OR (95% CI))	SDAI sustained remission (OR (95% CI))
Sustained T2T	**1.19 (1.03; 1.39)**	**1.23 (1.06; 1.44)**	**1.49 (1.24; 1.81)**	**1.45 (1.19; 1.77)**	**1.52 (1.27; 1.82)**

* All models adjusted for age, gender, disease duration and country. Sustained treat-to-target was considered followed if T2T was followed in ≥2 subsequent visits. T2T was considered being followed: i) if a patient had already a disease activity score below the target (DAS<1.6; DAS<2.4 for LDA definition) and treatment was correctly not intensified; or ii) if treatment was intensified upon a DAS≥1.6 (or DAS ≥2.4 for LDA definition). T2T: treat-to-target; DAS44: 44-joint disease activity score; DAS28-ESR: 28-joint disease activity score; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; CDAI: Clinical Disease Activity Index; SDAI: Simple Disease Activity Index; OR: odds ratio; CI: confidence interval.

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