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## EXTENDED REPORT

## Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update

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**ABSTRACT**

**Objective** A systematic literature review (SLR; 2009–2014) to compare a target-oriented approach with routine management in the treatment of rheumatoid arthritis (RA) to allow an update of the treat-to-target recommendations.

**Methods** Two SLRs focused on clinical trials employing a treatment approach targeting a specific clinical outcome were performed. In addition to testing clinical, functional and/or structural changes as endpoints, comorbidities, cardiovascular risk, work productivity and education as well as patient self-assessment were investigated. The searches covered MEDLINE, EMBASE, Cochrane databases and Clinicaltrials.gov for the period between 2009 and 2012 and separately for the period of 2012 to May of 2014.

**Results** Of 8442 citations retrieved in the two SLRs, 176 articles underwent full-text review. According to predefined inclusion/exclusion criteria, six articles were included of which five showed superiority of a targeted treatment approach aiming at least at low-disease activity versus routine care; in addition, publications providing supportive evidence were also incorporated that aside from expanding the evidence provided by the above six publications allowed concluding that a target-oriented approach leads to less comorbidities and cardiovascular risk and better work productivity than conventional care.

**Conclusions** The current study expands the evidence that targeting low-disease activity or remission in the management of RA conveys better outcomes than routine care.

**INTRODUCTION**

New treatment options and new treatment strategies have changed the achievable outcomes in rheumatoid arthritis (RA) over the last 20 years.<sup>1–5</sup> The treat-to-target (T2T) algorithm developed in 2010 consisted of 10 recommendations advocating the implementation of therapeutic principles, especially targeting remission or low-disease activity by adjusting therapy in the context of regular disease activity assessments. These recommendations were based on evidence obtained from a systematic literature review (SLR),<sup>6</sup> but to a large extent also on expert opinion. The international task force of the T2T project assumed that the evidence base for the T2T recommendations may have expanded and

further developed and that an update was needed especially to learn whether the expert-based statements were supported or contested by new evidence. Moreover, it was deemed interesting and important by the steering committee to not only focus on the traditional clinical, functional and structural endpoint but also on additional aspects related to quality of life and other outcomes important to patients.

**METHODS**

In 2012 and 2014, systematic literature searches of available evidence regarding the effects of treating RA strategically were conducted. In addition to testing clinical, functional and/or structural changes as endpoints, comorbidities, cardiovascular (CV) risk, work productivity and education as well as patient self-assessment were investigated. In the opinion of the steering committee, an initial search of the 2009–2012 literature performed in 2012 did not provide sufficient new evidence to justify an amendment of the recommendations. A new search on the literature published between 2012 and 5/2014 was now performed; that latter SLR focuses also on the additional outcomes mentioned above.

**SLR: UPDATE**

The new SLRs are a follow-up to the SLR performed by Schoels *et al* in 2009.<sup>6</sup> The search strategy developed then by the international steering committee of the T2T project and described in detail elsewhere<sup>6</sup> was expanded by using additional keywords (see below). Two research fellows (MMS in 2012; MAS in 2014) performed the SLRs with support from their mentors.

The definitions of the 2009 SLR were generally also used for this update (with slight changes). These were:

1. Strategy trial—clinical trial of any RA drug treatment, in which a clear outcome target was the primary endpoint and therapeutic consequences of failing to reach the target were predefined.
2. Targets—a target could be formulated by clinical, serological, patient reported, functional or imaging-derived variables; individual measures (eg, joint counts or acute phase reactants), composite scores (eg, disease activity score (DAS) or simplified disease activity index (SDAI)),

response criteria (eg, those defined by the American College of Rheumatology (ACR) or the European League Against Rheumatism (EULAR)), structural or ultrasound outcomes were considered alike.

3. Outcomes—clinical, functional, serological, structural changes and comorbidity, as defined in the respective trials, were compared between treatment groups.<sup>6</sup>

Beyond those applied in 2009, several new keywords: “patient-self assessment”, “comorbidities”, “cardiovascular risk”, “work productivity” and “education” in a target-oriented study were used. Controlled trials and observational studies were included. The searches covered the databases MEDLINE, EMBASE, Cochrane and Clinicaltrial.gov for the period between 1/2009 and 5/2014. The PICO (see online supplementary table S1) and the search strings are shown in the online supplementary material (see online supplementary table S2 for 2012, supplementary table S3 for 2014). Like in the previous work, the search was limited to human RA, adults and the English language. Furthermore, we did not exclude studies based on quality in the initial searches.

## RESULTS

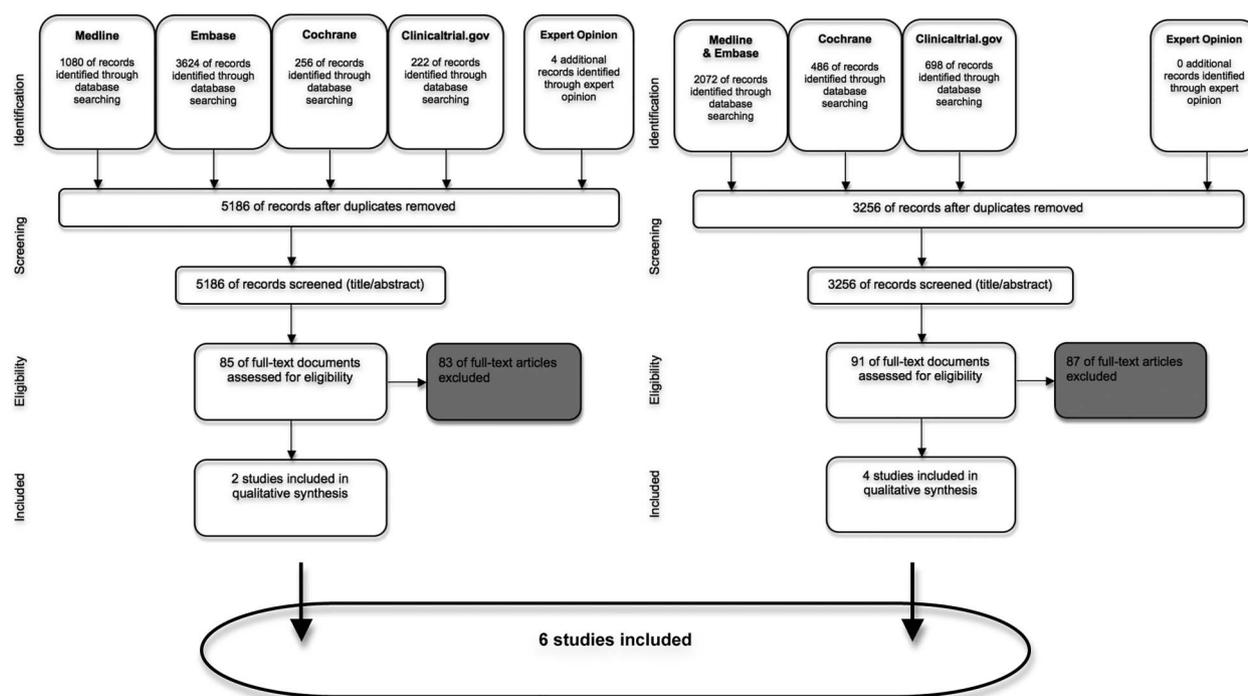
The first search performed in 2012 yielded 3256 hits. The search performed in 2014 arrived at 5186 records for further investigation (figure 1). Title and abstract review according to the inclusion/exclusion criteria led to assessment of eligibility of 91 and 85 full-text documents, respectively. The detailed review of the records in relation to the primary search objectives (comparison of primary endpoints in a priori strategy trials) resulted in the inclusion of four papers<sup>7–10</sup> from the search in 2012 and two additional papers<sup>11 12</sup> from the search performed in 2014. An overview of the six included studies is given in table 1A. From the identified references, we extracted information about the targets driving treatment decisions, the interval of control examinations, the numbers of patients included and the outcomes (table 1A).

Five of the six included studies dealt with early RA<sup>7–10 12</sup> and one trial with established RA.<sup>11</sup> All studies showed a superiority of a T2T strategy compared with routine care (RC)<sup>7 8 10–12</sup> except for one study (Strategic Reperfusion Early After Myocardial Infarction).<sup>9</sup> For the included studies, the risk of bias was assessed according to the scheme proposed by the ‘Cochrane risk of bias assessment’ (figure 2).

In early RA, the T2T strategy brought more patients into remission or low-disease activity and this was achieved more rapidly. Also, patients in the T2T group experienced larger improvements in patient assessments of pain, functional ability and disease activity (Dutch Rheumatoid Arthritis Monitoring (DREAM)).<sup>10</sup> In one trial of recent-onset active RA, the tight control approach showed that more patients achieved remission without disability and radiographic progression (Guérir la Polyarthrite Rhumatoïde Débutante (GUEPARD)/Etude et Suivi des Polyarthrites Indifférenciées Récentes (ESPOIR)).<sup>8</sup> Another study showed similar findings: the DAS-driven treatment led to better clinical outcomes (health assessment questionnaire, DAS28 and median erythrocyte sedimentation rate) and numerically, but not statistically different suppression of joint damage in the T2T group.<sup>7</sup>

In a study dealing with established active RA,<sup>11</sup> physicians were randomised into three groups (treating according to RC or targeting a DAS28 < 2.6 or a swollen joint count of 0). Although there was no difference in terms of therapeutic endpoint achievement, the time to reach a good/moderate EULAR response was significantly shorter and the dropout rates were significantly lower when using the targeted approaches.<sup>11</sup> Furthermore, using real-life data from the DREAM registry and the Nijmegen early RA inception cohort, a T2T strategy was found to be cost-effective compared with RC.<sup>12</sup>

Only one study did not show superior effects of a T2T strategy; however, this study assessed only a small number of patients with low radiographic damage and presented good functional status in both treatment groups.<sup>9</sup> Further studies are discussed in some more detail in the online supplement S4.



**Figure 1** Flow chart of the systematic literature search. Diagrammed are the results of the initial and second search (2012 and 2014, respectively) and the selection process of abstract screening, full-text review and inclusion according to expert opinion.

**Table 1** (A) Publications comparing an a priori targeted treatment strategy with routine care; (B) supportive evidence**(A) Studies directly addressing outcomes based on different treatment strategies**

Author	Groups	Treatment decision driving target	Interval of control examinations	N	Outcomes	Randomisation
Goekoop-Ruiterman <i>et al</i> <sup>7</sup>	Targeted group (T) Routine control group (R)	DAS $\leq$ 2.4 Treatment changes left to the discretion of the treating doctor	3 months 3 months	234 201	Clinical outcome at 1 year <i>Primary outcome</i> : change damage progression by the total SHS	Yes
Soubrier <i>et al</i> (GUEPARD/ESPOIR) <sup>8</sup>	GUEPARD— Targeted group (T) ESPOIR—Routine control group (R)	LDA by DAS28ESR $<$ 3.2	3 months Assessment at weeks 0, 24 and 52	65 130	<i>Assessed variables</i> : SJ, TJ, VAS pain, VAS general wellbeing, VAS physician overall assessment, morning stiffness, ESR, CRP, HAQ, radiographs hands and feet (SHS)	No
Van Eijk <i>et al</i> (STREAM) <sup>9</sup>	Targeted group (T) Routine control group (R)	DAS(44-joint score) $<$ 1.6 Treatment according to rheumatologist's preference	3 months 3 months	42 40	Clinical outcome at 2 years <i>Primary endpoint</i> : progression of radiographic joint damage at 2 years <i>Secondary endpoints</i> : difference between the two treatment strategies after 2 years regarding DAS, the percentage of patients in clinical remission (DAS $<$ 1.6), HAQ and adverse events	Yes
Schipper <i>et al</i> (DREAM) <sup>10</sup>	Targeted group (T) Routine control group (R)	DAS 28 $<$ 2.6 Treatment at the discretion of the treating rheumatologist	Assessment at weeks 0, 8, 12, 20, 24, 36 Assessment at weeks 0, 12, 24, 36, 52	126 126	Clinical outcome at 1 year <i>Primary endpoint</i> : percentage of patients in remission (DAS28 $<$ 2.6) <i>Secondary endpoint</i> : time to achieve remission, the course over time of the DAS28, the percentage of patients with "low" disease activity (DAS28 $\leq$ 3.2), the mean change in DAS28 and individual core set variables from baseline to 1 year	No
Pope <i>et al</i> <sup>11</sup>	DAS—targeted group (T)	DAS28 $<$ 2.6	Patients could be seen at any time as per judgement of the treating physician. Recommended visits were at 0, 2, 4, 6, 9, 12, 18 months	100	Clinical outcome at 1 year <i>Primary endpoint</i> : change in DAS 28 <i>Secondary endpoint</i> : changes at 6, 12, and 18 months in the SJ, TJC, CRP, ESR, HAQ, PGL, WLQ, patient satisfaction (5-point Likert scale), achievement of LDA (DAS $<$ 3.2), disease remission (DAS $<$ 2.6), and good/moderate EULAR response and time to achieve these end points	Cluster randomised
	0-SJC—targeted group (T)	0-SJC	Patients could be seen at any time as per judgement of the treating physician. Recommended visits were at 0, 2, 4, 6, 9, 12, 18 months	99		
	Routine control group (R)	Treatment left at the discretion of the treating physician	Patients could be seen at any time as per judgement of the treating physician. Recommended visits were at 0, 6, 12, 18 months	109		
Vermeer <i>et al</i> (DREAM) <sup>12</sup>	Targeted group (T) Routine control group (R)	DAS28 $<$ 2.6 Treatment left at the discretion of the rheumatologist	0, 8, 12, 20, 24, 36, 52 weeks 3 Months	261 213	The ICER per patient in remission and ICUR per QALY were calculated over two and 3 years of follow-up	No

**Panel (B) Supportive evidence for differences of outcomes depending on reaching different endpoints**

Author	Patients	Target/outcome	Conclusion	Randomisation
Targeting cardiovascular risk Crowson <i>et al</i> <sup>24</sup>	Review	n.a.	Suppression inflammation—may also reduce risk of heart disease; investigations of the innate and adaptive immune responses occurring in RA may delineate novel mechanisms in the pathogenesis of heart disease and help identify novel therapeutic targets for the prevention and treatment of heart disease Therapies used to treat RA may also affect the development of heart diseases, by suppressing inflammation, they may also reduce the risk of heart disease. Therapies used to treat RA may also affect the development of heart diseases, by suppressing inflammation, they may also reduce the risk of heart disease	Review

Continued

**Table 1** Continued**Panel (B) Supportive evidence for differences of outcomes depending on reaching different endpoints**

Author	Patients	Target/outcome	Conclusion	Randomisation
<b>Work/productivity</b>				
Rantalaiho <i>et al</i> <sup>20</sup>	195	Strict remission rates at 6, 12 and 24 months as well as the cumulative work disability days up to 5 years in these four subgroups	Using targeted treatment with monotherapy may well substitute for using combination DMARDs, but to benefit as many early RA patients as possible both approaches are necessary. Targeted treatment strategy is beneficial irrespective of the type of therapy	Yes
Smolen <i>et al</i> <sup>21</sup>	834 enrolled—604 eligible for double-blind period	Sustained LDA	Conventional or reduced doses of etanercept with MTX in patients with moderately active RA more effectively maintain LDA than does MTX alone after withdrawal of etanercept	Yes
Radner <i>et al</i> <sup>19</sup>	356	Physical function, health-related quality of life, work productivity, estimation of direct and indirect costs	Patient with remission show better function, health-related quality and productivity, even when compared with another good state, such as LDA. Also from a cost perspective, remission appears superior to all other states	No
<b>Education</b>				
Pope <i>et al</i> <sup>25</sup>	1000 serial RA charts	SDAI	Small group learning with feedback from practice audits is an inexpensive way to improve outcomes in RA	Cluster randomised
<b>Additional evidence</b>				
Thiele <i>et al</i> <sup>28</sup>	6864	DAS28 (Boolean/SDAI)	Patients fulfilling the new remission criteria tend to be not only free from active RA, but also from other disabling diseases. If these criteria are applied in clinical practice to guide treatment decisions, the impact of comorbidity should be taken into account	No
Vermeer <i>et al</i> <sup>29</sup>	409	DAS28, HAQ, SF36, MCS, SHS	In very early RA, T2T leads to high (sustained) remission rates, improved physical function and health-related quality of life, and limited radiographic damage after 3 years in daily clinical practice	No
Sakellariou <i>et al</i> <sup>30</sup>	166	SDAI, DAS28, HAQ, PDPS	The new remission definitions confirmed their validity in an observational setting and identify patients with better disease control.	No
Balsa <i>et al</i> <sup>31</sup>	97	SDAI	The results suggest that the SDAI classification of remission is closer to the concept of an absence of inflammatory activity, as defined by the absence of positive PD signal by US	No
Dale <i>et al</i> <sup>32</sup>	111	DAS44, HAQ, MRI (RAMRIS), X-ray hands + feet	MSUS disease activity assessment was not associated with improved clinical outcomes except a higher rate of DAS44 remission after 18 months. Target US sonographic remission does not appear to be superior to clinical LDA	Yes
Dale <i>et al</i> <sup>33</sup>	53	DAS28	Compared to the DAS28, global RA disease activity assessment using a limited MSUS joint set provided additional disease activity information and led to altered treatment decisions in a significant minority of occasions. This may allow further tailoring of DMARD therapy by supporting DMARD escalation in patients with continuing subclinical synovitis and preventing escalation in symptomatic patients with minimal clinical and/or ultrasonographic synovitis	No

CRP, C reactive protein; DAS, disease activity score; DMARD, disease-modifying antirheumatic drug; DREAM, Dutch Rheumatoid Arthritis Monitoring; ESPOIR, Etude et Suivi des Polyarthrites Indifférenciées Récentes; ESR, erythrocyte sedimentation rate; GUEPARD, Guérir la Polyarthrite Rhumatoïde Débutante; HAQ, health assessment questionnaire; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost utility ratio; LDA, low-disease activity; MCS, mental component summary; MSUS, musculoskeletal ultrasound; MTX, methotrexate; PDPS, power Doppler-positive synovitis; PD, power Doppler; PGL, patient global assessment of disease activity; QALY, quality-adjusted life-year; RA, rheumatoid arthritis; RAMRIS, rheumatoid arthritis MRI joint space narrowing score; SDAI, simplified disease activity index; SF36, short form 36 physical component summary; SHS, Sharp/van der Heijde radiographic score; SJ, swollen joint; SJC, swollen joint count; STREAM, Strategies in Early Arthritis Management TJ, tender joint; TJC, tender joint count; T2T, treat to target; US, ultrasound; VAS, visual analogue scale; WLQ, work limitations questionnaire.

**Figure 2** Risk of bias summary figure. +Low risk of bias, –High risk of bias, ?Unclear risk of bias, n.a. Not applicable. \*In the study of Pope *et al* physicians were randomised. \*\*Vermeer *et al* was comparing real life data from cohorts.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Blinding of outcome assessment (detection bias) (all-cause mortality)	Incomplete outcome data (attrition bias) (short-term [2-6 weeks])	Incomplete outcome data (attrition bias) (long-term [ > 6 weeks])	Selective reporting (reporting bias)
Goekoop-Ruiterman <i>et al</i> , 2010[7]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	+	+
Soubrier <i>et al</i> , 2011 (GUEPARD/ESPOIR)[8]	?	?	n.a.	n.a.	n.a.	n.a.	+	+
Van Eijk <i>et al</i> , 2012 (STREAM)[9]	?	+	+	n.a.	+	n.a.	+	+
Schipper <i>et al</i> , 2012 (DREAM)[10]	-	-	-	n.a.	+	n.a.	+	+
Pope <i>et al</i> , 2013 *[11]	?	?	?	?	?	?	?	+
Vermeer <i>et al</i> , 2013 (DREAM) **[12]	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	+

Regarding comorbidities, CV risk, work productivity or the role of (patient) education, none of the studies comparing T2T to RC had any of these outcomes as primary endpoint. However, these outcomes were addressed in observational data or registry studies comparing different strategic treatment approaches and endpoints, and therefore, these publications were regarded as further supporting evidence and are presented in table 1B.

Subanalysis of PREMIER (a multicenter, randomised, 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) and Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset (ASPIRE) data showed that the level of disease activity, the duration of SDAI remission and latency to remission all affect radiographic progression.<sup>13</sup> There is a direct relationship between disease activity and radiographic changes but a dissociation of the effect with tumour necrosis factor inhibitor use.<sup>14</sup> Among these publications were studies showing that Clinical Activity Disease Index remission is associated with lower CV risk and improved CV outcomes,<sup>15 16</sup> and the absence of swollen joints with improved overall survival.<sup>17</sup>

Additional studies that emerged during the SLR were categorised by topics and also presented to the task force. All these studies are listed in the online material (see online supplementary table S5).

Aside from the work of Pope *et al*,<sup>11</sup> all of the above-described articles studied patients with early RA. However, Gullick *et al*<sup>18</sup> investigated an observational cohort of patients with long-standing RA in a setting of usual care. In their study,

the authors compared the outcomes of an RA centre routinely using goal-directed therapy aimed at DAS28 < 2.6 with an age-matched and sex-matched sample of consecutive patients from other RA clinics. Significantly more T2T patients achieved the target, irrespective of their disease duration, and T2T led to significantly improved functional outcomes compared with RC.

## DISCUSSION

Since the original search informing the T2T task force, six new studies have been published, five of which fully support that a treatment strategy using a defined target conveys superior clinical, functional and structural outcomes compared with RC. In contrast to the data available in 2010, now more studies have used clinical remission defined by DAS or DAS28 as a main endpoint, which is a more stringent target than low-disease activity. While trials directly comparing potential differences in targeting remission versus low-disease activity are not available, supportive evidence exists that reaching ACR-EULAR remission is superior in terms of physical function, quality of life and work productivity and significant differences ensue when moving from one of these desired states to the other.<sup>19</sup>

In 2010, studies evaluating target-steered versus non-steered treatment approaches were only available for early RA. The new search revealed additional investigations on early or even recent-onset RA, but also data on established RA. Indeed, information on target steered therapy in established RA was a point in the research agenda in 2010; the data reveal that also in long-standing RA a T2T strategy is superior to RC.<sup>11 18</sup>

Finally, some new aspects were evaluated here, namely work productivity, comorbidities and effect of education on treatment

outcomes. While trials comparing different therapeutic strategies using these outcomes as primary endpoints are not yet available, secondary analyses reveal that lower disease activity is associated with better work productivity, less comorbidity and CV risk and that better education is likewise related to better clinical outcomes.<sup>11 15 16 19–25</sup> The task force was informed about these data as supportive evidence.

The present SLR provided new evidence regarding several items of the 2010 T2T recommendations,<sup>26</sup> which allowed to update the recommendations as presented in the paper by Smolen et al.<sup>27</sup> Indeed, the evidence base of several items increased from D to B or A (for details, see main paper) and several items, such as the overarching principle B and points 1 and 3 (with respect to established RA), as well as point 7, could be amended or expanded based on this new SLR. In conclusion, new and expanded evidence has been identified confirming that treating RA to a target of low-disease activity or remission enables patients to reach better outcomes than when they are exposed to RC. This information was provided to and discussed in detail by the task force allowing to develop an update of the T2T recommendations with much higher levels of evidence.<sup>27</sup>

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## Corrections

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Stoffer MA, Schoels MM, Smolen JS, *et al.* Evidence of treating rheumatoid arthritis to target: results of a systematic literature search update. *Ann Rheum Dis* 2016;**75**:16–22. In the second paragraph of the results section the acronym of the STREAM trial was erroneously defined as ‘Strategic Reperfusion Early After Myocardial Infarction’ rather than ‘Strategies in Early Arthritis Management’, as rightly mentioned in the legend of Table 1.

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