Proposed Metrics for the Determination of Rheumatoid Arthritis Outcome and Treatment Success and Failure

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ABSTRACT. ***Objective.*** Patients with rheumatoid arthritis (RA) and their physicians often disagree as to the success of RA treatment or RA outcomes. However, guidelines (such as EULAR criteria for DAS scores) are heavily weighted toward joint counts and laboratory tests, and no guidelines exist for patient reported outcomes. Our aims were (1) to provide a patient-based definition of successful RA outcome or of treatment success and failure; (2) to describe the characteristics of patients meeting this definition; (3) to describe how external states such as disability and comorbidity influence definitions of health outcome; and (4) to derive surrogate-measure cutpoints for the definition.

Methods. A total of 20,268 patients with RA (5132 without comorbidity) were studied by recursive partitioning and regression methods to determine best dividing points between RA treatment and outcome success and non-success using 0–10 visual analog scales (VAS) for patient global assessment, pain, fatigue, and RA activity, and a Health Assessment Questionnaire (HAQ) scale.

Results. 14.5% of all patients and 22.9% of those without comorbidity were very satisfied with their health (success). Patient global at a level ≤ 1.25 best separated success from failure. Mean and median scores for those who were very satisfied were HAQ (0–3 scale) 0.36, 0.12; pain (0–10) 1.1, 0.5; global (0–10) 0.9, 0.5; and fatigue (0–10) 1.5, 1.0. VAS scores increased by approximately 0.5 units for each comorbid condition.

Conclusion. Patient global at a level ≤ 1.25 best separates patients who are very satisfied with their health from those not very satisfied, regardless of the presence of comorbidity. All scores increase with increasing comorbidity, which must be accounted for when assessing individual patients. Values identified here suggest patients require better outcomes than are found in patients who are in Disease Activity Score-28 remission or OMERACT low disease activity states. (First Release Dec 1 2008; J Rheumatol 2009;36:27–33; doi:10.3899/jrheum.080591)

Key Indexing Terms:
TREATMENT FAILURE RHEUMATOID ARTHRITIS HEALTH SATISFACTION

Patients with rheumatoid arthritis (RA) and their physicians often disagree as to the success of RA treatment. Physicians employ a series of RA assessments that primarily rely on joint swelling and tenderness. The most widely accepted activity scale is the Disease Activity Scale-28 (DAS or DAS-28)[1]. The DAS score is determined by joint swelling and tenderness, erythrocyte sedimentation rate or C-reactive protein, and patient global severity. European League Against Rheumatism (EULAR) committees have determined that DAS-28 scores < 2.6 represent remission and < 3.2 represent low disease activity — presumably very good outcomes[1]. In another study a DAS score of 2.4 defined remission[2]. However, the correlation between DAS scores (and scale components) and patient self-reported scales, such as pain, global severity, and function, range only from fair to good[3].

Can a treatment be successful or can the outcome of RA be successful if the patient does not think so? Patients with low DAS scores may not be satisfied with levels of pain or functional impairment, or they may feel well and be satisfied even with a few swollen joints. Aside from the knowledge that lower scores are better than higher scores, there has not been a clear way to categorize treatment success or RA outcomes success in the metric of the patient.

In this report we identify levels of common patient variables that are most representative of treatment success and failure using patient assessments. Because there are no committees to determine success and failure for patient variables, we derive these measures from the patient variables themselves. In particular, we use the patient's assessment of satisfaction with health as the marker for successful outcome, after adjusting for comorbidity and demographic characteristics.

The specific study aims are: (1) to provide a definition of successful RA outcome or of treatment success and failure; (2) to describe the characteristics of patients meeting this definition; (3) to describe how external states such as dis-

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Supported by a grant from Bristol-Myers Squibb.

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Accepted for publication August 18, 2008.

ability and comorbidity influence definitions of health outcome; and (4) to derive surrogate-measure cutpoints for the definition.

MATERIALS AND METHODS

Study sample. Patients in this study were 20,268 adult participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of RA outcomes who were enrolled in the study from 1998 through 2007. NDB participants are recruited from the practices of United States rheumatologists and are followed prospectively with semiannual detailed 28-page questionnaires[4,5]. RA diagnoses were made by the 1244 referring rheumatologists. For most analyses we studied a single randomly selected observation from each patient. In analyses of treatment discontinuations we used multiple longitudinal observations per patient to examine the risk of treatment discontinuation.

In addition, for comparison of DAS-28 and patient data, we combined data from 2 previously described data sets. We used the Rheumatoid Arthritis Evaluation Study (RAES) data set[3] that contained patient and physician data on 669 RA patients collected in clinical practice, and the Arthritis and Rheumatology Clinic of Kansas (ARCK) data set of 406 similar observations[6].

Study variables. At each assessment we recorded demographic variables (age, sex, ethnic origin, and education level), treatment variables, and measures of work status and work disability. Comorbidity was measured by a patient-reported composite comorbidity score (range 0–9) comprising 11 present or past comorbid conditions including pulmonary disorders, myocardial infarction, other cardiovascular disorders, stroke, hypertension, diabetes, spine/hip/leg fracture, depression, gastrointestinal (GI) ulcer, other GI disorders, and cancer[7].

Satisfaction with health was evaluated with a 5-point scale[8]. The question asked was, "How satisfied are you with your health now?". Possible replies were very dissatisfied, somewhat dissatisfied, neither satisfied nor dissatisfied, somewhat satisfied, and very satisfied (Table 1). To investigate the relation of satisfaction with health to RA status and outcomes, we defined being very satisfied with one's health as a surrogate for treatment success. Not being very satisfied (not very satisfied) was interpreted as not a successful RA outcome or RA treatment outcome. We also use the term "health satisfaction" to indicate being very satisfied with one's health.

Five other patient self-reported variables were studied. Patients reported functional status using the Health Assessment Questionnaire (HAQ)[9,10]. We determined pain, global severity, and fatigue (over the last week) by visual analog scales (VAS)[11]. The VAS scales measure 21 points, from 0 to 10, at 0.5-unit intervals. The VAS line was not marked, and patients were unable to see their previous responses. The global question began, "Considering all the ways that your illness affects you, rate how you are doing on the following scale." Disease activity was assessed by the Rheumatoid Arthritis Disease Activity Index (RADAI)[12,13] question using a similar VAS scale. The specific question read, "In terms of joint tenderness and swelling, how active is your arthritis today?".

Table 1. Satisfaction with health in rheumatoid arthritis.

Measure	All Patients N = 20,268 Percent	CP	No Comorbidity N = 5132 Percent	CP
Very satisfied	14.5	14.5	22.9	22.9
Somewhat satisfied	36.4	50.9	41.8	64.7
Neither dissatisfied or satisfied	16.0	66.9	14.8	79.5
Somewhat dissatisfied	22.6	89.4	15.3	94.8
Very dissatisfied	10.6	100.0	5.2	100.0

CP: cumulative percentage.

Statistical methods. To determine the effect of health satisfaction (very satisfied) on the risk of treatment discontinuation, separate Cox time-varying regression analyses were used for groups treated with leflunomide (n = 6410), methotrexate (n = 15,349), hydroxychloroquine (n = 6706), etanercept (n = 4390), adalimumab (n = 2105), and infliximab (n = 6770).

To examine comorbidity and demographic predictors of health satisfaction, we used a generalized linear model (GLM) with a log link to estimate predictor risk ratios. The area under the receiver operating characteristic (ROC) curve was used as a measure of strength of association for the 5 predictive clinical variables[14]. Roughly, ROC values have an approximate interpretation of no value (0.50–0.60), poor (0.60–0.70), fair (0.70–0.80), good (0.80–0.90), and excellent (0.90–1.00). In correlation analyses the Pearson method was used.

We used recursive partitioning to determine the best cutpoints for each clinical variable using the RPART[15,16] and Random forest programs[17] in the R statistical package. The primary model to predict health satisfaction included age, sex, education level, ethnicity, comorbidity index, work disability, RA duration, prednisone use, analgesic use, global (severity), arthritis activity, pain, HAQ, and fatigue. Using the 1 standard error (SE) rule[15], only a single tree that included global was constructed. To determine cutpoints for pain, fatigue, HAQ, and arthritis activity, we ran 4 additional RPART analyses using each of these 4 variables as the only predictive variable. These analyses were repeated for the subset of patients who had no comorbidity.

Stata (version 10.0) was used for all other analyses[18]. A p-value of 0.05 (2-tailed) was selected as significant.

RESULTS

Satisfaction with health. As noted above, we defined being very satisfied with one's health as a surrogate for treatment success, and not being very satisfied as not a successful RA outcome or RA treatment outcome. Among all patients (n = 20,268), 14.5% were very satisfied with their health (Table 1). To accommodate the effect of other illnesses on health status, we performed a subanalysis on those patients with a comorbidity score of 0. Health satisfaction increased to 22.9% when the 5132 patients in this group were analyzed. This result is an estimate of the percentage of otherwise healthy patients whose overall perceived health is not affected by RA.

Relation of health satisfaction to physician and DAS measures. To place patient and nonpatient data in perspective, we analyzed data from 1075 RA patients from the RAES and ARCK datasets, where physician data and laboratory data were also available. The correlations between patient health satisfaction and other measures were patient global 0.676, physician global 0.487, and DAS-28 score 0.464. Figure 1 shows the distribution of DAS-28 scores among patients who are very satisfied and not very satisfied with their health. The vertical line at 2.6 represents the DAS remission level. These data indicate lack of agreement between patients' satisfaction with health and physician and DAS-28 scores. In patients achieving DAS-28 remission, mean and median clinical scores were: HAQ 0.50, 0.40, pain 2.43, 1.50, global severity 1.95, 1.50, and fatigue 3.01, 2.50.

Prediction of health satisfaction by comorbidity and demographic characteristics. In multivariable regression analysis, the relative risks (RR) for health satisfaction were: no

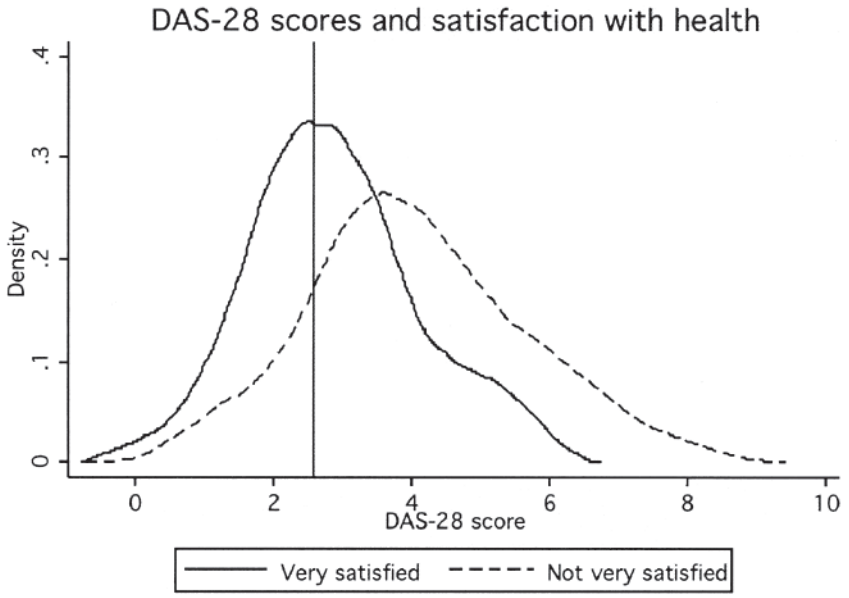

Figure 1. The distribution of DAS-28 scores in 1075 patients with RA who were very satisfied with their health compared with those who were not very satisfied with their health. The vertical line at 2.6 divides patients into those in remission and not in remission according to EULAR/DAS-28 criteria.

comorbidity versus any comorbidity RR 2.0 (95% CI 1.8–2.1), 10-year increase in age RR 1.1 (95% CI 1.0–1.1), college education RR 1.4 (95% CI 1.3–1.5), non-Hispanic White RR 1.5 (95% CI 1.3–1.6), and male gender RR 1.0 (95% CI 0.9–1.1). Adjusted for age, sex, college education, and ethnicity, the predicted probability of health satisfaction was 22.5% (95% CI 21.4%–23.7%) for patients without comorbidity compared with 11.5% (95% CI 11.0%–12.1%) for those with any comorbidity. The area under the ROC for this model was 0.622.

Characteristics of very satisfied and not very satisfied patients. Very satisfied patients had substantially less abnormal RA activity and severity scores (Table 2). In particular, they had very low mean and median scores for HAQ 0.36, 0.13, pain 1.1, 0.5, global severity 0.9, 0.5, RADAI RA activity 1.2, 0.5, and fatigue 1.5, 1.0.

Although their use of biologics and disease-modifying antirheumatic drugs was similar to those not satisfied (Table 2), they had substantially less use of corticosteroids, nonsteroidal antiinflammatory drugs, and opioid and all types of analgesics. In addition, among patients ≤ 62 years of age, more very satisfied patients were working (51.3% vs 45.3%) and fewer were disabled (2.1% vs 10.6%).

Nonsatisfaction with health also predicts treatment discontinuation. We hypothesized that people who were not very satisfied with their health would be more likely to discontinue RA treatment. For 6 common RA drugs we used time-varying Cox regression analysis to examine the predictive ability of not being very satisfied with health on the probability of treatment discontinuation for all causes and for lack of efficacy causes. The respective hazard ratios were leflunomide 1.5 (95% CI 1.3–1.8) and 1.6 (95% CI 1.2–2.0); hydroxychloroquine 1.2 (95% CI 1.0–1.4) and 1.4 (95% CI 1.1–1.7); methotrexate 1.4 (95% CI 1.3–1.6) and 1.4 (1.1–1.7); infliximab 1.7 (95% CI 1.4–1.9) and 1.7 (95% CI 1.4–2.2); etanercept 2.0 (95% CI 1.6–2.5) and 2.0 (95% CI 1.5–2.7); and adalimumab 1.6 (95% CI 1.2–2.2) and 1.8 (95% CI 1.1–2.7).

Determining cutpoints and test characteristics of RA activity and severity variables at the satisfied/not satisfied interface. Using recursive partitioning and multiple dependent variables (see Materials and Methods) in all patients and the subset without comorbidity, global severity was the only variable predictive of health satisfaction using the 1 SE rule. Tables 3A and 3B show the test characteristics of the predictive clinical variables. A global severity score ≤ 1.25 is the best predictor of treatment and RA success or non-success status. Global severity also had the best positive and negative predictive values. In the full model, only the 5 variables reported in Table 3A were selected by RPART for tree construction. Random forest analysis confirmed their importance, and comorbidity had limited importance and was eighth on the importance list. When the analyses were run on a subset of patients with no comorbidity, the global selection level was the same (Table 3B).

While the cutpoints described in Table 3A and 3B are suitable for groups of patients, they present problems in interpreting data on individual patients who may have a par-

Table 2. Characteristics of RA patients without comorbidity who are very satisfied with their health (N = 1174) and who are not very satisfied with their health (N = 3958).

Variable	Very Satisfied With Health	Mean	SD	Percentile 25th	50th	75th
RA severity/activity						
HAQ (0–3)	No	0.99	0.70	0.38	1.00	1.50
	Yes*	0.36	0.48	0.00	0.12	0.62
Pain (0–10)	No	3.7	2.6	1.5	3.0	5.5
	Yes*	1.1	1.5	0.0	0.5	1.5
Global severity (0–10)	No	3.4	2.3	1.5	3.0	5.0
	Yes*	0.9	1.5	0.0	0.5	1.0
RA activity (0–10)†	No	3.8	2.7	1.5	3.0	6.0
	Yes*	1.2	1.7	0.0	0.5	1.5
Fatigue (0–10)	No	4.1	2.8	2.0	4.0	6.5
	Yes*	1.5	1.9	0.0	1.0	2.0
Employed (%)	No	45.3				
	Yes*	51.3				
Disabled (%)	No	10.6				
	Yes*	2.1				
Lifetime TJR (%)	No	13.3				
	Yes*	11.1				
Treatment						
Biologic (%)	No	35.4				
	Yes	35.9				
DMARD (%)	No	80.5				
	Yes*	77.7				
Any NSAID (%)	No	67.5				
	Yes*	57.8				
Prednisone (%)	No	37.7				
	Yes*	22.9				
Any analgesic (%)	No	36.5				
	Yes*	20.9				
Opioids (%)	No	15.8				
	Yes*	5.5				
Demographics						
Age (years)	No	57.0	13.6	47.5	56.9	67.1
	Yes	56.7	13.3	46.9	57.0	67.1
Sex (% male)	No	23.7				
	Yes	21.4				
College graduate (%)	No	27.6				
	Yes*	35.8				
Non-Hispanic White (%)	No	95.0				
	Yes	96.3				

† From Rheumatoid Arthritis Disease Activity Index (RADAI). * $p < 0.05$.

ticular level of comorbidity. Figure 2 shows that for all patients the 25th percentile scores of most VAS scales increased by approximately 0.5 units for each comorbidity class. The HAQ increased by 0.1, 0.2, 0.3, and 0.4 for increasing comorbidity classes. With this information, we can approximate the cutpoint for the VAS scales in Table 3B by adding 0.5 to the VAS score cutpoint for each comorbidity. For example, a patient with 2 comorbid conditions is in a "treatment success" state, accounting for comorbidity, if her global score is ≤ 2.25.

DISCUSSION

The primary purpose of our study was to propose and describe a reasonable definition for RA outcome and RA treatment success and non-success based on patient data, and then to describe levels of clinical variables that could be used to identify this outcome. While being very satisfied with one's health is an arbitrary definition, it is also a reasonable one. Subsequent research may come up with another definition, but the current work represents a starting point.

All binary outcomes that are based on dichotomizing a continuous state are arbitrary, even if they are reasonable, including the DAS-28 levels identified by EULAR. And all have problems. Altman and Royston indicate that in dichotomizing continuous states, "one may seriously underestimate the extent of variation in outcome between groups, such as the risk of some event, and considerable variability may be subsumed within each group. Individuals close to

Table 3A. Surrogate clinical separating points for satisfaction with health in all patients (n = 20,268).

Variable	Cutpoint	Sensitivity (%)	Specificity (%)	PPV	NPV	ROC
Global	≤ 1.25	71.3	87.0	48.1	94.7	0.78
Pain	≤ 1.25	63.2	86.1	43.6	92.8	0.75
Fatigue	≤ 1.75	63.5	83.7	39.7	93.1	0.74
HAQ	≤ 0.625	72.4	74.2	32.3	94.1	0.73
Activity*	≤ 0.75	48.3	90.8	47.1	91.2	0.70

Table 3B. Surrogate clinical separating points for satisfaction with health in patients with no comorbidity (n = 5132).

Variable	Cutpoint	Sensitivity (%)	Specificity (%)	PPV	NPV	ROC
Global	≤ 1.25	78.7	79.9	53.8	92.7	0.79
Pain	≤ 1.25	70.4	80.5	51.7	90.2	0.75
Fatigue	≤ 1.25	71.3	75.3	46.2	89.8	0.73
HAQ	≤ 0.50	74.7	67.3	40.4	90.0	0.71
Activity*	≤ 1.25	54.7	87.8	57.1	86.7	0.71

* Measured by Rheumatoid Arthritis Disease Activity Index (RADAI). PPP: positive predictive value; NPV: negative predictive value; ROC: receiver operating characteristic.

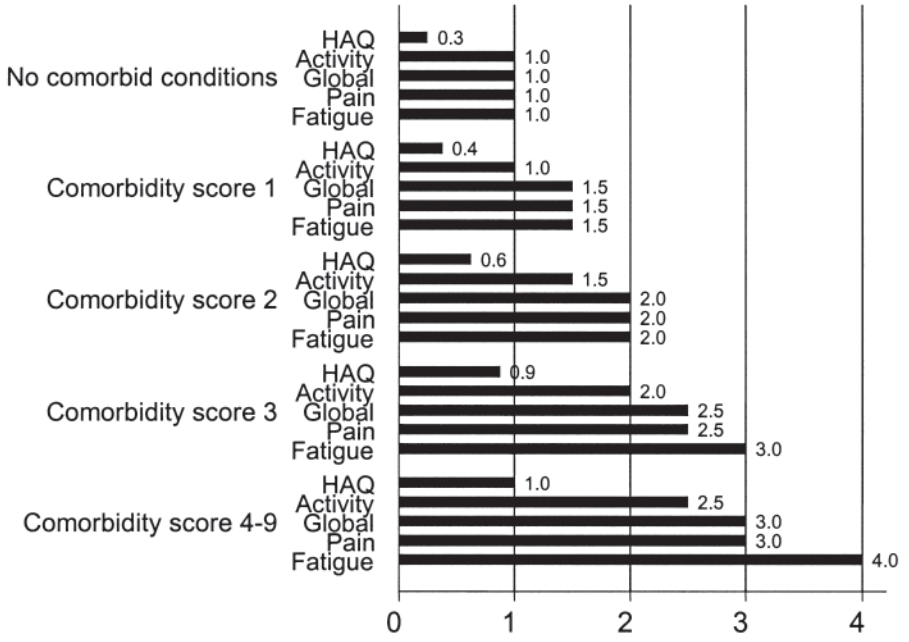

Figure 2. Effect of comorbidity on patient clinical scores at the 25th percentile of each score (all patients). For VAS scales, the scores increase approximately 0.5 units for each additional comorbidity.

but on opposite sides of the cutpoint are characterized as being very different rather than very similar"[19]. In addition, measurement error is often around a half a standard deviation for most scales[20,21]. Therefore, it is important to use the guidelines for cutpoints of clinical variables proposed here as approximate values.

For patients with RA who are very satisfied with their health, mean and median clinical variable scores are very low: HAQ 0.36, 0.13, pain 1.1, 0.5, global severity 0.9, 0.5, RADAI RA activity 1.2, 0.5, and fatigue 1.5, 1.0. These values are different from the values that best separate very satisfied and not satisfied states. Such values are HAQ ≤ 0.625, pain ≤ 1.25, global ≤ 1.25, activity ≤ 1.75, and fatigue < 1.75.

Wells, *et al*, in their report on low disease activity, suggested values from the American College of Rheumatology core set that could be used to define low disease activity, including VAS pain ≤ 2, HAQ ≤ 0.5, and patient global

≤ 2[22]. The values given in our report are slightly lower (except for the HAQ) than those noted by the Wells group. This is not surprising, as they were trying to define low disease state, while health satisfaction might be closer to a remission state. On the other hand, when we examined the data from the RAES and ARCK databases, patients in DAS-28 remission had mean and median scores as follows: HAQ 0.50, 0.40, pain 2.43, 1.50, global severity 1.95, 1.50, and fatigue 3.01, 2.50. Taken together, at least from the perspective of patient data, the clinical values identified here, and the separating values (cutpoints) suggested here as a measure of health satisfaction, are lower than those seen in patients experiencing DAS remission and low disease activity. We can interpret this as suggesting that DAS remission and low disease activity are not fully satisfying states for patients with RA.

The use of "health satisfaction" rather than RA activity is a potential limitation to our approach. Patients with comorbidity could theoretically drive up the cutpoint (something that is only a limited problem with scales like the DAS-28). However, recursive partitioning analyses show that not to be the case when the full sample or those with no comorbidity are studied. In addition, RA damage rather than activity might also influence the cutpoint level. However, HAQ did not contribute additional information to the recursive partitioning analyses of the full dataset analyses. Nor did RA duration, disability, work status, or use of prednisone or analgesics. These data suggest that global severity can be used as a guide to RA status and treatment success.

As with all data from groups of patients, extrapolation to individual patients must be done with caution. Based on regression analyses (not shown) and the data of Figure 2, it seems reasonable to advance the cutpoints by 0.5 units for each comorbid condition when seeking a placement rule for a patient. The association of patient scores with comorbidity has been described by others as well[23]. The values identified by this study must be seen as approximate because of individual patient differences. Even so, this method helps to define levels of treatment and outcomes success from the perspective of the patient.

The correlation of 0.464 between DAS-28 and patient global is important; not so much because it shows lack of agreement — rather, its importance is that it identifies an additional dimension in RA outcome. In the end, patients must not only have few swollen and tender joints, and normal laboratory tests, but also must feel well. It is not whether one approach to RA measurement is better than the other, but that both are required.

With so many outcome scales available, it may be asked, "What is the outcome we need to care about most?". For clinicians, the DAS, Clinical DAI, Simplified DAI, and their individual components provide us with semiobjective information about RA activity; imaging studies provide some information about structural damage, the HAQ some insight into functional status; and there are pain and fatigue scales, too, in addition to the patient global scale. Regulatory agencies, third-party payers, health economists, and epidemiologists may be interested in still other outcomes. But clinical care, as indicated above, requires the use of RA activity assessments and requires an awareness of how patients perceive their health and their RA.

When we go beyond the individual patient and try to understand the outcomes of treatment in the community, patient measures become even more important. Individual HAQ and pain scores are difficult to interpret; but the knowledge that 14.5% of all patients and 22.9% of those without comorbidity were very satisfied with their health is important and clear. In the age of new biologic therapies, the question "Can a treatment be successful or can the outcome of RA be successful if the patient doesn't think so?" helps to put the results of treatment and the outcome of RA into perspective.

In summary, patient global at a level ≤ 1.25 best separates patients who are very satisfied with their health from those not very satisfied, regardless of the presence of comorbidity. VAS pain, fatigue, and RADAI activity and HAQ perform somewhat less well. All scores increase with increasing comorbidity, which must be accounted for at the individual patient level. The values identified here suggest patients require better outcomes than are found in patients experiencing DAS-28 remission or OMERACT (Outcome Measures in RA Clinical Trials) low disease activity states.

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