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The clinical status and economic savings associated with remission among patients with rheumatoid arthritis: *Leveraging linked registry and claims data for synergistic insights*

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Abstract

Introduction—Treat to target guidelines recommend achieving remission or low disease activity in rheumatoid arthritis (RA). However, the reduction in adverse events (AEs) and costs associated with lower disease activity is unclear.

Methods—We used CORRONA linked to Medicare data to identify RA patients. Time varying disease activity was measured using Clinical Disease Activity Index (CDAI); outcomes included all-cause hospitalization, a composite of hospitalization or emergency department (ED) visits, mortality, and medical costs. Outcome-specific Cox proportional models evaluated the adjusted hazard ratios (aHR) between disease activity and outcomes, controlling for potential confounders including comorbidities grouped into 4 patient phenotypes. Costs were analyzed with mixed models using a Gaussian distribution with log transformation.

Results—Depending on outcome, 4,593 RA patients contributed up to 12,001 person years. Median age was 71 years, 75% women. At baseline, approximately 50–60% of patients were in remission or low disease activity (LDA). There was a dose-response relationship between RA disease activity (remission, low, moderate, high) and the incidence of hospitalizations (13.1, 17.8, 21.2, 27.5 per 100py, respectively); all aHR were significant: 0.68 (remission), 0.87 (low), and 1.24 (high) compared to moderate disease activity. Similar trends were observed for ED visits and mortality. The crude difference in annual medical costs between remission (\$11,145.65) and moderate disease activity (\$17,646.49) was \$–6,500.84; the adjusted difference(95 % CI) was \$ –3,133.07 (–4737.72, –1528.43).

Conclusion—Leveraging the benefits of linking registry and administrative data together, lower disease activity in RA was associated with incrementally reduced risks of all-cause hospitalization, ED visits, mortality, and medical costs in a dose-dependent fashion.

Keywords

rheumatoid arthritis; disease activity; registry; Medicare; administrative claims

Introduction

Treat to target guidelines for patients with rheumatoid arthritis (RA) recommend to tailor treatment to achieve a state of remission, or at least low disease activity (1–3). The merits of achieving these low disease activity targets might seem self-evident to rheumatologists but may be less clear to other stakeholders. As many as half of RA patients starting a biologic fail to attain a state of remission or low disease activity, despite experiencing some clinical improvement (e.g. an ACR50 response, or clinically relevant improvement in the Disease Activity Score) (4). However, some evidence suggests that for such individuals, patient reported outcomes (PROs) may be improved even further if remission or LDA can be attained (5).

The benefits of lower disease activity states on other important outcomes including serious adverse events (e.g. hospitalizations) and emergent healthcare services (e.g. visits to the emergency department [ED]) are uncertain. Conversely, it is possible that tighter control of disease activity may have unintended consequences if more intensive management is required, including treatment with multiple immunosuppressive medications, which could put patients at greater risk for side effects. Given that more intensive strategies often entail use of expensive RA therapies, the economic impact of more aggressive RA treatments to achieve more intensive disease activity targets is not clear. Finally, it may be difficult for patients to accept acceleration of treatment given concerns regarding perceived risk of toxicity. Physicians need to be able to deconstruct these fears with tangible examples of the benefits of lower disease activity in terms that will be meaningful for patients.

As a first step to understand whether remission or low disease activity might have an impact on safety outcomes and associated costs, we evaluated clinical and economic outcomes associated with lower disease activity states using data from the U.S. CORRONA RA registry, with a linkage to administrative data for outcome ascertainment. We hypothesized that lower disease activity would be associated with fewer ED visits, a lower likelihood of all-cause hospitalization, a lower risk for all-cause mortality, and lower healthcare costs. Our analysis also serves as an example of a linkage between an outpatient disease registry and administrative claims to address a scientific question for which both types of data would be required.

Methods

Data source and eligible patient population

The CORRONA registry is an independent, prospective observational cohort of patients with RA. Patients are recruited from more than 165 private and academic practice sites across 40 states in the United States, with 625 participating rheumatologists, with median patient follow-up of 2.9 years.

CORRONA registry patients were eligible if they had rheumatologist-confirmed RA and contributed at least 2 visits to the registry. CORRONA data were linked to administrative data from the U.S. Medicare system (n=4,876) using methods previously described (6). Patients were allowed to enter into follow-up on the date when they met both of the following criteria 1) date of their second CORRONA visit and 2) the date of six month of full observability/coverage (Medicare part A [inpatient] and B [outpatient], and not having part C [Medicare Advantage]) coverage (n=4,750). These requirements ensured a complete history available in both the registry and linked Medicare medical data. The final analysis population included those who had full information in the registry necessary to characterize their RA and associated comorbidities (n=4,593), as described below. All patients provide consent to participate in the registry, and the Medicare data was governed by a data use agreement from the Center for Medicare and Medicaid Services.

RA Disease Activity

Using registry data, the main independent variable of interest was disease activity which was measured by the Clinical Disease Activity Index (CDAI) (7), a commonly used metric that does not require a lab to be available in real time. If one of four components of CDAI was missing, that same component of the previous visit's CDAI was carried forward, conditional on it not being missing. The area under the curve (AUC) of the CDAI was calculated at the start of follow-up and updated at the time of each registry visit, computed using the trapezoidal rule that calculated the mean CDAI between each pair of registry visits, and weighted by the amount of time between visits. This measure is described hereafter as the cumulative time-weighted average CDAI. For visit intervals that extended beyond 6 months, the CDAI was imputed using the geometric mean between the prior visit and the next visit. In the main analysis, CDAI was modeled using this method, and in a sensitivity analysis, the CDAI from only the most recent registry visit was used as the main exposure variable. Additional analyses substituted each of the 4 CDAI components for the composite CDAI to compare the strength of association between them for each of the 4 outcomes.

Clinical and Economic Outcomes

The three clinical outcomes of interest included inpatient hospitalization, a composite of inpatient hospitalization or ED visit, and all-cause mortality. Medicare data include healthcare encounter billed for by the healthcare system, and also capture vital status and date of death but not cause of death. As a fourth outcome of interest, healthcare costs were computed using the allowed amounts actually reimbursed to healthcare systems by the Center for Medicare and Medicaid Services (CMS), excluding the cost of parenterally administered biologics for RA that billed under part B. A subgroup analysis restricted the cohort to individuals who had part D for the entirety of their follow-up time. In this subgroup of patients, we re-examined the cost outcome and included not only medical costs, but also the costs of parenterally administered biologic drugs (from Medicare part B) as well as part D outpatient drug costs. Costs were calculated as 2016 Medicare-paid amounts and were adjusted for inflation based on the Medical Care component of the Consumer Price Index.

Comorbidity

Patients with a higher burden of comorbidities might have a differential likelihood to reach lower disease activity states, and the observed disease activity and outcome associations might differ in sicker people and yield confounding of our main exposure-outcome associations. Therefore, we classified patients into distinct comorbidity groups using both registry and Medicare data. Information from the registry included number of past DMARDs including biologics, the number of non-biologic DMARDs, the mHAQ, steroid dose group (none, < 7.5mg/day, ≥ 7.5mg/day), and physician-assessed RA disease severity on a 1–4 ordinal scale. Comorbidities and healthcare utilization from the Medicare data included the Charlson comorbidity score (8, 9), the sum of the 34 Elixhauser comorbidity index conditions (10), the number of physician visits, the number of hospitalizations, the number of unique medication classes as defined by the American Society of Health System Pharmacist (AHFS) classification, disability as formally assigned by Medicare as the original reason for entitlement, the sum of the 254 AHRQ Clinical Classification Software (CCS) conditions (11), an adapted comorbidity score applicable to rheumatic disease patients, the Rheumatic Disease Comorbidity Index (12), and total healthcare costs paid by Medicare. All registry-derived covariates were assessed at the visit at which follow-up began (baseline), and in the Medicare data, in the 6 months prior to baseline.

Because the methods described above that assess the severity of illness were anticipated to have appreciable collinearity and shared variance, we reduced the dimensionality of these conditions through principal components analysis (13). This method reduced the variance shared between the 14 illness measures and created a series of orthogonal principal components vectors. The proportion of variance explained was described according to the number of principal components. K-means clustering was then applied to the principal components vectors to identify comparable patient phenotypes grouped on the basis of the severity of their comorbidities, with a goal of deriving 4 clusters. For the clustering procedure, twenty random starts were used so as to avoid finding a non-robust local optimum, and the best selected based upon minimization of the mean squared error. The clusters were then plotted 3 dimensionally on the axes of the first 3 principal components vectors.

Statistical analysis

The eligible patient cohort was characterized descriptively by comorbidity patient phenotype. The extent of missingness in key variables was low (CDAI 2.3% of visits; glucocorticoid dose 1.7%, comorbidity phenotype 3.0%) and complete case analysis was used without imputation. The incidence rates (IRs) of ED visits, hospitalization, and death then were calculated for each category of RA disease activity, remission, low, moderate, and high, using published CDAI cutpoints (7). Ninety-five percent confidence intervals for the IRs were calculated using a Poisson distribution (14). We also enumerated the top ten primary diagnosis codes associated with inpatient hospitalizations, the composite of hospitalization and ED visits (not resulting in hospitalization), and as a proxy for cause of death for the mortality outcome, the subgroup of hospitalizations where the patient died during the hospitalization or in the next 30 days. Date of death but not cause of death was available in this data so these diagnoses were used as proxies for cause of death. This

approach is consistent with past epidemiologic studies that define ‘fatal MI’ or ‘fatal stroke’ as MI or stroke events that are followed by death within 28–30 days(15).

Cox proportional hazards modeling was used to estimate each of the outcomes of interest, updating the cumulative, time-weighted average CDAI at each CORRONA visit, and using it as the predictor variable for the ensuing visit interval. In each of the three separate event analyses (one per outcome), follow-up time was censored at the time of the first event. Censoring also was applied if there was a gap of more than 12 months between CORRONA visits, more than one missing CDAI component, death or other reason for termination in the registry, or the end of follow-up in Medicare (loss of Medicare AC coverage, or 12/31/2012). In the sensitivity analysis, censoring was not applied if CDAI was missing, but rather, the person-time associated with missing CDAI was excluded until a non-missing CDAI was available from the registry. In all models, moderate disease activity was referent given that a large fraction of RA patients remain in moderate disease activity despite the availability of effective RA therapies (4). This analysis was intended to inform the potential benefits of better disease activity states, including both low disease activity or remission. The cost data were analyzed with mixed models using a Gaussian distribution with a log transformation. Based on factors hypothesized to be potential confounders between RA disease activity and the outcomes of interest, each model adjusted for comorbidity cluster membership, age, sex, RA disease duration, RA seropositivity, and glucocorticoid use. Model discrimination was assessed using the c index(16, 17), similar to the c statistic in a logistic regression model (18, 19). All analyses were conducted using SAS 9.4.

Results

Among the 4,750 RA patients potentially eligible for analysis, 4,593 were included. The majority of the drop in sample size was due to missingness in current steroid dose (n=78), mHAQ (n=47), and physician-assessed severity of RA (n=20), assessed at the start of follow-up in the registry. Seven of the principal components vectors in the PCA explained more than 80% of the variance in the assessments of comorbidity and illness severity. Using k-means clustering, there were 4 distinct clusters of patients formed with good discrimination, as shown in Figure 1. The corresponding patient characteristics are described in Table 1. The least ill group of patients was in Cluster 1 and the most ill in Cluster 4. Compared to cluster 1, cluster 2 represented somewhat younger patients (mean age 66 years) who had worse mHAQ scores (0.63 units vs. 0.26 units), had longer RA disease duration (18 vs. 11 years), were less likely to be on MTX (46% vs. 76%), and more likely to be on a biologic (63% vs. 39%) and glucocorticoids (33 vs. 23%). They were more likely to be disabled (49% vs. 22%) and had higher prevalence of comorbidity-related variables. Compared to cluster 1, patients in clusters 3 and 4 were more typical Medicare age and had a higher prevalence of all comorbidities, with cluster 4 patients being the smallest group and having the highest burden of comorbidities.

The number of events and incidence rates of the 3 clinical outcomes of interest are shown in Table 2. In the analysis using time-weighted cumulative CDAI (Table 2, top half), there were 1819 hospitalizations, 2499 hospitalization or ED visits, and 313 deaths. Patients in remission had the lowest rate of all three types of events, and a strong dose-response

relationship between disease activity category and event incidence rate was observed. The same trends were observed in annual costs. Patients in remission had the lowest annual medical costs (\$11,145.65) and those in high disease activity had the highest costs (\$20,449.91), a crude difference of \$9,304.26. The difference between remission and moderate disease activity was \$6500.84/year. Results were very similar when the most recent visit's CDAI was used (Table 2, bottom half). The incidence rate of hospitalization stratified by comorbidity cluster membership is shown in Figure 2. A dose response relationship was observed, with higher rates of hospitalization occurring as disease activity increased, and as the comorbidity cluster group ranged from the least ill patients to the most ill patients. Patients within each cluster contributed to all 4 disease activity groups. However, patients in the least ill comorbidity group (cluster 1) contributed 87% of their exposure time to the remission or the low disease activity categories, whereas patients in the other 3 cluster categories contributed 57–78% of their exposure time to the remission or low disease activity categories.

The top 10 diagnoses associated with the inpatient and emergency department visits and hospital associated mortality are shown in Table 3. Hospitalizations and ED visits for osteoarthritis/joint replacement, infections, and cardiovascular conditions were the most common categories of events. Of the 313 deaths, 206 (66%) occurred within 30 day of hospital admission. The most common primary hospitalization diagnoses associated with these fatalities were septicemia, respiratory failure, and pneumonia, and stroke events.

Table 4a describes the multivariable-adjusted association between RA disease activity and various outcomes. As shown, and after adjustment for potentially confounding factors including comorbidity cluster membership, patients in remission and low disease activity consistently had significantly lower event rates for each event type compared to patients in moderate disease activity. Remission was associated with a 32% lower rate of all cause hospitalization, a 24% lower rate of ED visits or hospitalization, and a 37% lower rate of mortality. For the hospitalization model, the c index of a model with age alone was 0.55 and increased to 0.62 after adding the comorbidity clusters, and to 0.64 with the CDAI, and improved negligibly after including all remaining covariates. In the separate cost model, remission was associated with \$3133.07/year lower healthcare costs compared to patients in moderate disease activity. Of the 4 components of the CDAI, the patient global was the statistically strongest predictor in all models in Table 4; it was significant when substituted for the CDAI, and remained significant when the other 3 CDAI components were also included (not shown).

The magnitude of benefit associated with low disease activity (compared to moderate) was smaller and associated with a 13% low rate of hospitalization and 13% ED/hospitalizations, and a 15% lower rate of mortality, and \$1,629 lower annual costs. Glucocorticoid dose consistently was associated with higher rates of all outcomes and higher costs. There was no interaction between CDAI category and cluster membership ($p > 0.20$ for each interaction term). The adjusted results from the sensitivity analysis that used only the most recent CDAI were similar (Appendix Table 1).

The subgroup analysis of RA patients who had part D medication coverage over their entire follow-up (n=1,445 patients) estimated both medical costs and medication costs, for both parenteral drugs (e.g. infused biologics) and outpatient medications. Over the entire follow-up period, the distribution of biologic-exposed person time varied by disease activity category and was 40% (remission), 45% (low disease activity), 51% (moderate) and 52% (high disease activity). Patients in remission incurred annual costs of \$25,148.05, which after adjustment, was \$4,718.08 per year less than patients in moderate disease activity (Appendix Table 2).

Discussion

In this analysis of older RA patients participating in a large U.S. registry with a linkage to Medicare administrative data, we observed significantly lower rates of hospitalizations, ED visits, mortality and medical costs associated with remission. Those in low rather than moderate disease activity likewise had lower associated rates of hospitalization and mortality, although the magnitude of the difference was smaller. As expected, those in high disease activity states had the highest rates of all outcomes and the greatest healthcare costs. Given that many patients initiating biologics improve but reach only moderate disease activity rather than low or remission disease states, our findings provide additional support for the treat to target goals recommended by international and U.S. guidelines (1, 2).

Our results are consistent with prior literature showing lower risks for specific medical events associated with better (lower) disease activity states. A study by Crowson et. al. studied 525 RA patients and found lower rates of CVD associated with patients in remission and among those who did not have a recent RA flare (20). Prior results from the CORRONA registry that included not only older but also younger RA patients found a lower rate of myocardial infarction, stroke, and CHD death for those in lower disease activity states (21). Additionally, results from the British Society of Biologic Registry found that patients receiving anti-TNF therapy had a lower risk of myocardial infarction, but only if they achieved lower disease activity (22).

Our grouping of comorbidities using principal components analysis and k-means clustering yielded distinct groups of RA patients with different phenotypes and took advantage of the availability of comorbidity information from both registry and claims data sources. Cluster 1 included RA patients who were relatively healthy with a low prevalence of comorbidities, similar to most other RA disease cohorts (23). Cluster 2 might be characterized as younger, largely disabled patients with longstanding RA and represents a unique group of RA patients, many of whom qualify for Medicare eligibility on the basis of disability rather than age. Clusters 3 and 4 were older RA patients with high comorbidity burdens. While cluster membership was strongly associated with each of the outcomes, even for patients in remission, there was no statistical evidence for effect modification by cluster.

The medical costs associated with being in a lower disease activity state deserve mention. The incremental cost savings associated with being in remission (\$11,145) compared to moderate disease activity (\$17,646) was \$6,501/year (crude) and \$3,133 (adjusted). In purely economic terms, if a patient required a biologic to move from moderate disease activity to

remission, the lower medical costs associated with being in remission would not be offset by the high cost of biologic therapy, typically >\$30,000/year. While the forthcoming availability of biosimilar medications is likely to substantially reduce biologic costs, they still are unlikely to make continued use of a biologic cost-saving for a health plan. However, although biologics may not be cost saving in the short term, the incremental potential benefits on patient's near-term quality of life, work productivity, downstream reduction of progression of underlying comorbidities, reduction in future joint damage and disability etc. are additional benefits that were not explicitly represented in this analysis.

The strengths of our study include the ability to examine outcomes using a relatively novel integrated data source that linked administrative claims to a large U.S. outpatient disease registry to conduct an analysis that neither data source alone could accommodate. Additionally, our focus on older patients and relatively large sample size yielded adequate power to study serious adverse event-related differences between disease activity states. We controlled for multiple comorbidity indices derived both from registry and administrative data sources. The methods implemented to characterize discrete patient phenotypes based upon their comorbidity burden appeared useful and might be a desirable framework to consider for future studies, particularly when multiple types of data are available, such as a registry linked with health plan data.

Several design features of our study should be considered in interpreting our results. First, we used registry data linked to administrative data from Medicare, a program that typically enrolls older patients (age ≥ 65) or those with disabilities, including RA. As such, these results may not be generalizable to younger RA patients. We also recognize that the deterministic methods used to link to the administrative data did not link all RA patients in CORRONA with Medicare, although prior work has shown only small differences between linked and not linked patients (6). Additionally, as in all observational analyses, results may be subject to misclassification and residual or unmeasured confounding. This is particularly relevant in being able to adequately adjust for comorbidities, which despite being ascertained both from the registry and administrative claims data, are presumably imperfectly measured in both. We also recognize that while we did not find a significant interaction between CDAI and the comorbidity phenotype, this analysis may have been underpowered to detect this effect modification. Finally, despite our attempts to use reasonable methods to control for multimorbidity, we cannot rule out the possibilities of residual confounding, informative censoring or reverse causation (i.e. that we are observing the effect of multimorbidity on AEs and costs).

In conclusion, we found that better RA disease activity states were associated with lower rates of hospitalizations, ED visits, mortality and medical costs. While results from this observational study should be interpreted cautiously and causal relationships not inferred, these findings do provide information regarding safety benefits potentially able to be achieved for patients who achieve lower disease activity states, along with associated savings in healthcare costs.

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Appendix

Appendix Table 1

Multivariable-Adjusted Association between Time-Varying RA Disease Activity Measured by most recent visit's CDAI and Various Outcomes (n=4,593)

	Adjusted* Hazard Ratio
All-cause hospitalization	
Disease Activity	
Remission	0.65 (0.57, 0.75)
Low Disease Activity	0.82 (0.73, 0.91)
Moderate Disease Activity	1.0 (referent)
High Disease Activity	1.16 (1.00, 1.34)

	Adjusted* Hazard Ratio
Steroids	
None	1.0 (referent)
Low (< 7.5mg/day)	1.21 (1.09, 1.34)
High (>= 7.5mg/day)	1.40 (1.15, 1.70)
Emergency Department Visit or All-cause hospitalization	
Disease Activity	
Remission	0.72 (0.64, 0.81)
Low Disease Activity	0.84 (0.76, 0.92)
Moderate Disease Activity	1.0 (referent)
High Disease Activity	1.11 (0.98, 1.26)
Steroids	
None	1.0 (referent)
Low (< 7.5mg/day)	1.16 (1.06, 1.27)
High (>= 7.5mg/day)	1.21 (1.01, 1.45)
Death	
Disease Activity	
Remission	0.61 (0.43, 0.85)
Low Disease Activity	0.90 (0.69, 1.17)
Moderate Disease Activity	1.0 (referent)
High Disease Activity	1.09 (0.76, 1.56)
Steroids	
None	1.0 (referent)
Low (< 7.5mg/day)	1.80 (1.43, 2.27)
High (>= 7.5mg/day)	2.05 (1.33, 3.16)
Cost, \$ per year (mean 95% CI)	
Disease Activity	
Remission	-3,153.04 (-4,409.05, -1,897.04)
Low Disease Activity	-1,486.48 (-2,533.94, -439.02)
Moderate Disease Activity	1.0 (referent)
High Disease Activity	1534.16 (90.26, 2978.06)
Steroids	
None	1.0 (referent)
Low (< 7.5mg/day)	2,618.73 (1,441.81, 3,795.66)
High (>= 7.5mg/day)	7,394.20 (4,885.27, 9,903.14)

* adjusted for age, gender, sero-positivity, CDAI, comorbidity cluster membership, and RA disease duration

Appendix Table 2

Crude and Multivariable-Adjusted Association between Cumulative Weighted RA Disease Activity Measured by CDAI and Totals Costs, among Subgroup of Patients with Medicare Part D Coverage (n=1,445)

	Crude Mean Costs, \$ per year (95% CI)	Adjusted* Mean Costs, \$ per year (95% CI)
Disease Activity		
Remission	25,148.05 (21,831.91, 28,464.18)	-4,718.08 (-9,412.23, -23.93)
Low Disease Activity	27,832.28 (26,494.22, 29,170.34)	-4,555.03 (-7,864.09, -1,245.96)
Moderate Disease Activity	36,378.14 (34,147.67, 38,608.60)	1.0 (referent)
High Disease Activity	41,385.40 (37,908.70, 44,862.10)	1,225.27 (-3,445.70, 5,896.24)

* adjusted for age, gender, sero-positivity, CDAI, comorbidity cluster membership, and RA disease duration

Figure 1.
Comorbidity-related patient phenotypes derived from k-means clustering plotted on first 3 principal component vectors
Cluster numbers refer to the categories in Table 1: Cluster 1 (black), Cluster 2 (red), Cluster 3 (blue), Cluster 4 (green)

Figure 2.
Rate of Hospitalization Associated with RA Disease Activity Category and Comorbidity Cluster

Table 1

Characteristics* of Eligible CORONA participants linked to Medicare (n=4593)

	Least III				Most III	
N	Cluster 1 2,608	Cluster 2 896	Cluster 3 941	Cluster 4 148		
Registry-Derived Characteristics						
Age, mean (SD)	70.61 (8.64)	65.93 (10.31)	71.16 (9.05)	70.24 (9.98)		
median (IQR)	71.00 (66.00, 76.00)	67.00 (60.00, 73.00)	72.00 (66.00, 78.00)	72.00 (66.00, 77.50)		
Sex- Female	1941 (74.4%)	711 (79.4%)	678 (72.1%)	112 (75.7%)		
CDAL, %						
Remission	680 (26.1%)	101 (11.2%)	153 (16.3%)	18 (12.1%)		
Low Disease	973 (37.3%)	284 (31.7%)	335 (35.6%)	39 (26.4%)		
Moderate	575 (22.0%)	269 (30.0%)	260 (27.6%)	45 (30.4%)		
High	249 (9.5%)	212 (23.6%)	153 (16.3%)	35 (23.6%)		
Missing [†]	131 (5.0%)	30 (3.3%)	40 (4.2%)	11 (7.4%)		
mHAQ, mean (SD)	0.26 (0.36)	0.63 (0.54)	0.49 (0.52)	0.74 (0.58)		
median (IQR)	0.13 (0.00, 0.38)	0.50 (0.13, 1.00)	0.38 (0.00, 0.88)	0.63 (0.25, 1.13)		
RF or Anti-CCP, %						
Either positive	1210 (46.4%)	439 (49.0%)	425 (45.2%)	67 (45.3%)		
Negative	125 (4.8%)	21 (2.3%)	51 (5.4%)	8 (5.4%)		
Missing	1273 (48.8%)	436 (48.7%)	465 (49.4%)	73 (49.3%)		
RA Disease Duration, years	11.82 (10.97)	18.23 (11.05)	12.09 (10.86)	16.05 (12.57)		
	8.00 (3.00, 17.00)	17.00 (10.00, 25.00)	9.00 (4.00, 18.00)	14.00 (6.00, 23.00)		
Current Medications						
MTX	1992 (76.4%)	416 (46.4%)	607 (64.5%)	77 (52.0%)		
Infliximab	523 (20.1%)	185 (20.6%)	164 (17.4%)	20 (13.5%)		
Etanercept	255 (9.8%)	142 (15.8%)	93 (9.9%)	11 (7.4%)		
Adalimumab	158 (6.1%)	105 (11.7%)	49 (5.2%)	7 (4.7%)		
Certolizumab pegol	0	1 (0.1%)	1 (0.1%)	1 (0.7%)		
Golimumab	3 (0.1%)	2 (0.2%)	1 (0.1%)	0		

		Least Ill		Most Ill	
N		Cluster 1 2,608	Cluster 2 896	Cluster 3 941	Cluster 4 148
Tocilizumab		2 (0.1%)	3 (0.3%)	0	0
Abatacept		58 (2.2%)	90 (10.0%)	40 (4.3%)	6 (4.1%)
Rituximab		22 (0.8%)	35 (3.9%)	26 (2.8%)	2 (1.4%)
Any biologic use		1023 (39.2%)	565 (63.1%)	376 (40.0%)	48 (32.4%)
Daily prednisone dose, %					
None		2025 (77.6%)	563 (62.8%)	634 (67.4%)	91 (61.5%)
≤7.5mg		518 (19.9%)	260 (29.0%)	247 (26.2%)	40 (27.0%)
>7.5mg		65 (2.5%)	73 (8.1%)	60 (6.4%)	17 (11.5%)
AHRQ CCS Comorbidity Count		6.89 (3.47)	8.19 (4.30)	14.94 (4.76)	25.74 (7.22)
CORRONA Comorbidity Index		7.00 (4.00, 9.00)	8.00 (5.00, 11.00)	14.00 (11.00, 18.00)	25.00 (21.00, 29.00)
Physician-assessed severity of RA (1–4 ordinal scale)		1.23 (0.47)	1.38 (0.60)	1.75 (0.83)	1.77 (0.94)
Cost, \$/6 months		1.00 (1.00, 1.00)	1.00 (1.00, 2.00)	2.00 (1.00, 2.00)	1.00 (1.00, 2.00)
		2.42 (1.05)	3.21 (1.07)	2.55 (1.08)	2.90 (1.08)
		2.00 (2.00, 3.00)	3.00 (3.00, 4.00)	3.00 (2.00, 3.00)	3.00 (2.00, 4.00)
		4138 (5230)	7016 (8084)	9601 (8494)	45756 (29155)
		1769 (781, 5877)	4073 (1125, 10696)	6800 (3127, 13437)	39116 (26032, 55501)
Medicare-Derived Characteristics, n(%)					
Diabetes		187 (7.2%)	82 (9.2%)	355 (37.7%)	57 (38.5%)
COPD		97 (3.7%)	55 (6.1%)	241 (25.6%)	49 (33.1%)
Number of Physician Visits		5.95 (3.22)	7.13 (4.08)	12.53 (5.31)	23.87 (10.98)
Hospitalizations		5 (4.00, 8.00)	6 (4.00, 9.00)	12 (9.00, 15.00)	22 (16.00, 28.50)
None		2550 (97.8%)	842 (94.0%)	707 (75.1%)	3 (2.0%)
1		56 (2.1%)	51 (5.7%)	223 (23.7%)	28 (18.9%)
>=2		2 (0.1%)	3 (0.3%)	11 (1.2%)	117 (79.1%)
Disabled**		582 (22.3%)	442 (49.3%)	325 (34.5%)	56 (37.8%)
Charlson Comorbidity Index		1.18 (0.47)	1.28 (0.54)	2.54 (1.10)	3.38 (1.54)

	Least III			Most III
N	Cluster 1 2,608	Cluster 2 896	Cluster 3 941	Cluster 4 148
Elixhauser Comorbidity Index	1 (1.00, 1.00) 1.86 (0.92) 2.00 (1, 2)	1 (1.00, 2.00) 2.04 (1.06) 2.00 (1.00, 3.00)	2.00 (2.00, 3.00) 4.39 (1.38) 4.00 (3.00, 5.00)	3.00 (2.00, 5.00) 6.71 (2.34) 6.00 (5.00, 8.00)
Rheumatic Disease	1.01 (1.09)	1.11 (1.15)	3.58 (1.39)	4.49 (1.70)
Comorbidity Index	1 (1.0, 2.0)	1.00 (0.00, 2.00)	4.00 (3.00, 4.00)	4.00 (3.50, 6.00)
Number of unique *** medications	2.67 (3.69)	3.43 (4.58)	5.74 (6.17)	6.51 (7.10)

Note: comorbidity-related covariates with continuous data are shown as mean (SD) on the first line, and median (25th/75th percentile) on the second line.

* Measured as the start of follow-up at the registry visit, or in the administrative data in the 6 months prior to start of follow-up

† patients may have had missing CDAI at the start of follow-up but subsequently contributed person-time once CDAI was available at a later registry visit

** as classified by Medicare as the original reason for coverage

*** defined by AHFS drug class, among the subgroup of people who also had Medicare part D coverage.

Table 2

Crude Rates* of Outcomes, by RA Disease Activity Associated with RA Disease Activity

Disease Activity Category by Cumulative, Time-Averaged CDAI (n=4353)	Hospitalization	ED Visit or Hospitalization	Death	Inpatient and Outpatient Medical Costs, annualized \$
Events, n	1,819	2,499	313	
Person-time, years	9,668.11	7,546.81	13520.91	
Remission (<=2.8)	13.1 (11.5, 15.0)	25.9 (23.4, 28.7)	1.5 (1.0, 2.1)	11,145.65 (10507.14, 11784.16)
Low (2.8–10)	17.8 (16.6, 19.1)	30.8 (28.9, 32.7)	2.3 (1.9, 2.7)	14,518.83 (13880.17, 15157.49)
Moderate (10–22)	21.2 (19.5, 23.0)	37.2 (34.6, 39.9)	2.7 (2.2, 3.2)	17,646.49 (16724.60, 18568.38)
High (>22)	27.5 (24.2, 31.2)	46.7 (41.9, 52.1)	2.8 (2.0, 3.8)	20,449.91 (19035.85, 21863.97)
Disease Activity Category by most recent visit's CDAI (n=4593)	Hospitalization	ED Visit or Hospitalization	Death	Inpatient and Outpatient Medical Costs, annualized \$
Events, n	1,934	2,642	331	
Person-time, years	10301.39	8,049.27	14458.05	
Remission (<=2.8)	13.6 (12.3, 15.0)	25.6 (23.6, 27.8)	1.5 (1.2, 2.0)	10,702.52 (9820.35, 11584.69)
Low (2.8–10)	17.9 (16.6, 19.2)	31.3 (29.4, 33.3)	2.4 (2.0, 2.8)	14,024.37 (13438.26, 14610.47)
Moderate (10–22)	22.6 (20.8, 24.6)	38.7 (35.9, 41.6)	2.7 (2.2, 3.3)	17,530.73 (16714.09, 18347.36)
High (>22)	26.9 (24.0, 30.2)	44.7 (40.4, 49.5)	2.8 (2.1, 3.7)	20,050.84 (18671.54, 21430.13)

* Rate per 100py

Table 3

Ten Most Common Primary Diagnoses associated with Inpatient Hospitalization and Emergency Department Visits and Hospital-Associated Deaths

Inpatient Hospitalization (n=1960)	Inpatient Hospitalizations or ED Visits (n=2667)	Top 10 Hospital Diagnoses Associated with Mortality (n=206)*
Osteoarthritis/Joint Replacement (9.7%)	Osteoarthritis/joint replacement (5.3%)	Septicemia (21.2%)
Back problem (5.8%)	Chest pain (4.5%)	Respiratory failure (8.3%)
Pneumonia (5.2%)	Back problem (4.4%)	Pneumonia (5.3%)
Septicemia (4.1%)	Pneumonia (3.3%)	Acute stroke (4.4%)
Coronary atherosclerosis (3.2%)	Abdominal pain (3.2%)	Lung cancer (4.4%)
COPD (3.1%)	Superficial injury (3.0%)	Heart failure (4.4%)
Dysrhythmia (3.1%)	Dysrhythmia (2.7%)	Acute MI (3.9%)
Device-related complications (2.8%)	Sprain (2.4%)	COPD (3.9%)
RA (2.7%)	COPD (2.4%)	Secondary malignancy (2.4%)
Acute myocardial infarction (2.5%)	Fracture of arm (2.3%)	Aspiration pneumonitis (1.9%)

ED = emergency department; CVD=cardiovascular disease; MI = myocardial infarction, COPD = chronic obstructive lung disease

* where death occurred in the hospital or within 30 days (n=206, 66% of all 315 deaths)

Table 4

Multivariable-Adjusted Association between Cumulative Weighted RA Disease Activity Measured by CDAI and Various Outcomes (n=4,353)

	Adjusted* Hazard Ratio
All-cause hospitalization	
Disease Activity	
Remission	0.68 (0.58, 0.80)
Low Disease Activity	0.87 (0.78, 0.97)
Moderate Disease Activity	1.0 (referent)
High Disease Activity	1.24 (1.07, 1.45)
Steroids	
None	1.0 (referent)
Low (< 7.5mg/day)	1.19 (1.07, 1.32)
High (>= 7.5mg/day)	1.38 (1.13, 1.69)
Emergency Department Visit or All-cause hospitalization	
Disease Activity	
Remission	0.76 (0.67, 0.87)
Low Disease Activity	0.87 (0.79, 0.96)
Moderate Disease Activity	1.0 (referent)
High Disease Activity	1.21 (1.06, 1.37)
Steroids	
None	1.0 (referent)
Low (< 7.5mg/day)	1.15 (1.05, 1.26)
High (>= 7.5mg/day)	1.20 (1.00, 1.44)
Death	
Disease Activity	
Remission	0.63 (0.42, 0.95)
Low Disease Activity	0.85 (0.66, 1.09)
Moderate Disease Activity	1.0 (referent)
High Disease Activity	1.13 (0.77, 1.65)
Steroids	
None	1.0 (referent)
Low (< 7.5mg/day)	1.88 (1.48, 2.39)
High (>= 7.5mg/day)	2.16 (1.40, 3.35)
Mean Cost, \$ per year, mean (95% CI)	
Disease Activity	
Remission	-3,133.07 (-4,737.72, -1,528.43)
Low Disease Activity	-1,629.51 (-2,814.61, -444.41)
Moderate Disease Activity	1.0 (referent)
High Disease Activity	1,000.43 (-777.96, 2778.81)

	Adjusted* Hazard Ratio
Steroids	
None	1.0 (referent)
Low (< 7.5mg/day)	2,541.72 (1,313.26, 3,770.18)
High (>= 7.5mg/day)	7,787.13 (5,210.81, 10,363.44)

* adjusted for age, gender, sero-positivity, CDAI, comorbidity cluster membership, and RA disease duration