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Trends and Determinants of Osteoporosis Treatment and Screening in Patients with Rheumatoid Arthritis Compared to Osteoarthritis

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Abstract

Objective—To profile osteoporosis (OP) care in patients with rheumatoid arthritis (RA) over the past decade.

Methods—Patients with RA or osteoarthritis (OA) were followed from 2003 through 2014. OP care was defined as receipt of OP treatment (with exception of calcium/vitamin D) or screening (OPTS). Adjusted trends over follow-up, and the factors associated with OP care were examined using the multivariable Cox proportional hazards.

Results—OPTS was reported in 67.4% of 11,669 RA and 64.6% of 2,829 OA patients during a median (IQR) 5.5 (2–9) years follow-up. In patients for whom treatment was recommended by the 2010 ACR glucocorticoid-induced OP (GIOP) guidelines (48.4% of RA and 17.6% of OA patients), ~55% overall reported OP medication use. RA patients were not more likely to undergo OPTS compared to OA patients, HR (95%CI) 1.04 (0.94–1.15). Adjusted models showed a stable trend for OPTS between 2004 and 2008 compared to 2003 with a significant downward trend after 2008 both in RA and OA patients. Factors associated with receipt of OP care in RA patients were older age, postmenopausal state, prior fragility fracture or diagnosis of OP, any duration of glucocorticoid treatment, and biologic use.

Conclusion—About half of RA patients for whom treatment was indicated never received a OP medication. OP care in RA patients was not better than OA patients, and the relative risk of application of this care has been decreasing in RA and OA patients since 2008 without improvement after the release of the 2010 ACR GIOP guideline.

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Keywords

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INTRODUCTION

Rheumatoid arthritis (RA) is associated with a two-fold increased risk of osteoporosis (OP), even at younger ages (1–4). The underlying reasons include accelerated aging and hormonal changes, physical disability, and most importantly inflammation-associated osteoclast activation (5–7). Glucocorticoid (GC) use, a well-established cause of secondary OP, is also common in RA (8). The adverse consequences of GC on bone health are particularly problematic in RA patients due to the heightened risk of OP with an increased hip and vertebral fracture risk even in the absence of GC use (9). Osteoporotic fractures significantly contribute to the functional loss, morbidity, mortality, and health-related costs of RA (10–12). Furthermore, fracture-related morbidity and mortality are substantially higher in RA patients than the general population (13). Therefore, it is of great importance to appropriately assess the OP/fracture risk and apply preventive and therapeutic care to RA patients.

Despite not being RA-specific, the American College of Rheumatology (ACR) published in 2010 glucocorticoid-induced osteoporosis (GIOP) prevention and treatment guidelines to increase awareness and treatment for GIOP (14). It recommends calcium/vitamin D supplementation and using the World Health Organization (WHO) Fracture Risk Assessment Tool (FRAX) (15) for all patients initiating GC (14). Bisphosphonates (teriparatide on some occasions) are recommended for patients with high fracture risk regardless of GC dose and duration; patients with medium-fracture risk taking <7.5 mg/day prednisone for ≥3 months, and, regardless of FRAX scores, patients taking ≥7.5 mg/day of prednisone for ≥3 months (14). These recommendations were only for postmenopausal women, men age ≥50 years, and younger age groups with a previous fragility fracture (14).

Based on the 2010 ACR GIOP guideline recommendations, it was estimated that among GC-receiving US adults, 65% of postmenopausal women and 52% of men age ≥50 years were at sufficient risk for GIOP-related fracture to warrant OP treatment (16). However, the proportion of at-risk patients receiving bisphosphonate treatment rates was below 30% (16). Although adherence to this guideline was not separately reported for RA patients, the overall OP treatment requirement and therapeutic gap may be even larger in RA patients since many who are not on GC may still be at sufficient fracture risk to warrant OP treatment based on the National Osteoporosis Foundation (NOF) or other OP guidelines (17, 18).

Despite the well-known burden of OP-related fractures and incorporation of more aggressive RA treatment strategies including biologic disease-modifying antirheumatic drugs (bDMARDs), the prevalence of OP in RA leading to fracture remains high (19). Therefore, the need for OP screening and treatment interventions for RA patients remains higher than the general population. However, it is unknown whether the therapeutic advancements in RA and release of the 2010 ACR GIOP guidelines improved OP care of RA patients compared to the patients who were at relatively lower risk for OP such as patients with non-

inflammatory rheumatic diseases. By using a US-wide observational cohort we assessed the frequency, trends, and predictors of OP treatment and screening in patients with RA compared to patients with osteoarthritis (OA) from 2003 through 2014.

PATIENTS and METHODS

Patients were participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal prospective observational study. Participants were primarily recruited from rheumatologists and were followed with self-report semi-annual questionnaires (20). Adult patients with RA or OA who completed ≥2 semiannual questionnaires from January 2003 through December 2014 were included. OA patients with coexistent RA or other inflammatory diseases excluded. Follow-up continued until the participant was censored at death, loss to follow-up, or end of study period.

The primary outcome was “OP treatment or screening (OPTS)” defined as undergoing bone mineral density (BMD) measurement or the receipt of any OP treatment reported by the patients. OP treatments included oral/parenteral bisphosphonates, raloxifene, teriparatide, and hormone replacement therapy (HRT). As denosumab was received by only one patient, it was not included in OPTS. Since the 2010 ACR GIOP guideline recommended some of the bisphosphonates (alendronate, risedronate and zoledronic acid) or teriparatide for the GIOP prevention and treatment, we determined a secondary outcome called OPTS-ACR, which included only these four medications in addition to BMD testing. Examined separately, calcium/vitamin D supplementation was not included as an OP medication.

Treatment exposure was measured at NDB enrollment and every six months. GC treatment was examined categorically in 4 groups, not-using (reference), <3 months, 3–12 months, and >12 months. To examine the association of DMARDs with the outcomes, we created four mutually exclusive hierarchical DMARD groups: 1. Methotrexate (MTX) monotherapy (reference), 2. Any TNF-α inhibitor (TNFi), 3. Any non-TNFi bDMARD, and 4. Others.

Fracture risk determination

Ten-year fracture probabilities of patients were assessed with the US version of FRAX® tool (version 4.0) (http://www.shef.ac.uk/FRAX) without BMD results (15, 21). This approach uses clinical risk factors (gender, race, age, body mass index [BMI], prior fragility fracture, parental history of hip fracture, current tobacco smoking, ever long-term GC use [≥5mg/day prednisone >3months], RA, other causes of secondary OP and daily alcohol consumption of ≥3units/day) to estimate the 10-year probability of a major osteoporotic fracture (MOF) (hip, clinical spine, forearm or humerus) or hip fracture alone. As the parental history of hip fracture was not available for the NDB, the missing data was generated by simulations based on the conditional probability of the association of a risk factor with age, BMI, and other dichotomous clinical variables by logistic regression (22) (see online supplement). Using this method, parental history of hip fracture was estimated as 6% of the entire cohort.

A FRAX score of ≤10% for a 10-year MOF was regarded as low-risk, 10–20% medium-risk and ≥20% high-risk. OP treatment candidates according to the 2010 ACR GIOP and the 2014 NOF guidelines were determined. Both guidelines were developed similarly using the

RAND/UCLA appropriateness method which combines systematic literature review and expert opinion with a rating for appropriateness. Treatment indications by the ACR GIOP guideline were: postmenopausal women and men age ≥50 years who had high fracture risk by FRAX or history of fragility fracture (fragility fracture recommendation was also applied to GC-receiving younger age groups) regardless of GC dose and duration; had medium-risk and taking <7.5mg/day prednisone for ≥3 months; taking ≥7.5 mg/day of prednisone for ≥3 months regardless of their FRAX score. Treatment indications by the NOF guideline which allows assessing all patients, including GC non-users, were applied without BMD results: postmenopausal women and men age ≥50 years who had a previous hip or vertebral fracture or 10-year hip fracture probability of ≥3% or MOF probability of ≥20% by FRAX (17).

Statistical analysis

Baseline characteristics of RA and OA patients were compared using chi-square, Student's t, Wilcoxon signed-rank, or Mann-Whitney U tests, as appropriate. The percentages of patients tested with BMD, treated with an OP treatment, or calcium/vitamin D were determined according to fracture risk category. Crude incidence rates for outcomes were calculated by dividing the number of events by the corresponding person-time at risk.

The Andersen-Gill multiple failure Cox proportional hazards models were used to determine adjusted trends of and factors associated with OPTS (23). Several models with different covariates were examined, and the model with the best goodness-of-fit, the lowest Akaike information criterion (AIC) (24) was chosen as the final model. This model included the following variables: age groups (<40 years-reference, 40–49 years, 50–64 years, ≥65 years), gender (premenopausal-reference, postmenopausal women and men), location of residence (rural vs. urban), education level (years), insurance type (any vs. none), rheumatic disease comorbidity index (25) excluding fracture, prior fragility fracture or diagnosis of OP, FRAX 10-year MOF risk categories, disease duration, Health Assessment Questionnaire (HAQ), hierarchical DMARD group, GC exposure, calendar year (2003-reference), BMI in WHO categories (26), and annual influenza vaccination as a proxy measure of healthcare utilization (27). The final model was stratified by the primary physician for arthritis (rheumatologist vs. other). Since ethnicity and smoking history were included in the FRAX risk and had no influence on the outcomes and model fit, the final model did not include these variables.

In sensitivity analyses, BMD testing or receipt of any OP treatments were examined as separate outcomes to explore whether predictors of screening and treatment differed. Frequencies and predictors of OP treatment were also assessed after excluding HRT which might have been prescribed for indications other than OP. As a subgroup analysis, the final model was reexamined in RA patients after excluding premenopausal women and men age <50 years who never used GC. The model for this analysis included age and age-squared instead of the age group to deal with the non-linear relationship of age with the outcomes in this elderly subgroup.

All assessed treatment exposures and disease severity measures were treated as time-dependent covariates. To prevent bias from removing observations due to missing data, all missing covariates (variables had <1% missing) were replaced by using multiple imputations

by chained equations to create multiple imputed datasets for analyses (28). All tests were two-sided and considered statistically significant when $P<0.05$. All statistical analyses were performed using Stata version 14.0 (StataCorp, College Station, TX, USA).

RESULTS

The study cohort consisted of 11,669 RA and 2,829 OA patients. Baseline characteristics of RA and OA patients are shown in Table 1.

During a median (IQR) follow-up of 5.5 (2.3–9.0) years in RA and 5.5 (2.1–9.1) years in OA, OPTS and OPTS-ACR were reported in 67.4% and 61.8% of RA patients and 64.6% and 56.7% of OA patients, respectively. The incidence rates for both outcomes were similar in RA OA patients (Table 2). Less than half of RA and OA patients (43% overall) reported either receipt of BMD testing or OP medication during their first observations. In patients without prevalent OPTS (N=6,611 for RA, N=1,617 for OA, Table S1), the total event numbers and incidence rates of both outcomes were much lower compared to the entire cohort but were again similar in RA and OA patients (Table 2).

Overall, in RA patients the frequency of calcium/vitamin D supplementation was 64%, BMD testing 58%, receipt of any OP treatment 44%, ACR-recommended medications 26%, and OP treatment excluding HRT 30%. In OA patients, except for calcium/vitamin D supplementation, OP screening and treatment frequencies were slightly lower than RA patients (Table 3). OP treatment and screening frequencies were much higher in high fracture risk patients by FRAX, although ~35% of high-risk RA and OA patients never received any OP treatment (Table 3, Table 2S). Applying the 2010 ACR GIOP guidelines, 48.4% of RA (53.8% of postmenopausal women and 44.5% of men age ≥50years) and 17.6% of OA patients (19.3% of postmenopausal women and 11.4% of men age ≥50years) were identified as potential candidates to receive OP treatment. However, treatment with any OP medication and ACR-recommended OP medication were 55% and 37%, respectively, both in RA and OA patients (Table 3). When the NOF guideline recommendations were applied, 49.3% of RA (54.3% of postmenopausal women and 47.6% of men age ≥50years) and 51.4% of OA patients (54.8 % of postmenopausal women and 41.2% of men age ≥50years) were considered as OP treatment candidates. In this group, OP treatment was reported in 54.5% of RA and 49.8% of OA patients. Additionally, 21% of RA patients who would be recommended an OP treatment by the 2014 NOF guideline were considered as ineligible by the 2010 ACR GIOP guideline due to GC nonuse while 19% of RA patients who met the criteria for OP treatment by the 2010 ACR GIOP guideline were considered low risk by the 2014 NOF guideline due to higher dose and longer duration GC exposure regardless of the FRAX category.

In fully adjusted models, RA patients compared to OA patients were not more likely to undergo OPTS, HR (95%CI) 1.04 (0.94–1.15), or OPTS-ACR, HR 1.05 (0.96–1.15). Adjusted models also showed a stable trend for OPTS and OPTS-ACR in both RA and OA patients between 2004 and 2008 compared to 2003 (Figure 1). However, following 2008, a significant downward trend was observed for both outcomes without any meaningful improvement after the release of the 2010 ACR GIOP guideline (Figure 1). The same

downward trend after 2008 was also observed for BMD testing and OP treatment receipt as separate outcomes and in RA subgroups including postmenopausal women and men age ≥50 years, GC-exposed, and bisphosphonate non-exposed patients (data not shown).

In the examination of predictors for OP care in RA, older age, postmenopausal state, having insurance, higher education level, urban residency, immunization for influenza, prior fragility fracture or diagnosis of OP, and any duration of GC treatment (more prominent with longer durations) were associated with undergoing OPTS and OPTS-ACR (Table 4). Male and overweight/obese RA patients were less likely to undergo either OPTS or OPTS-ACR. Regarding DMARDs, receiving any TNFi or non-TNFi bDMARDs compared to MTX monotherapy was also associated with better OPTS and OPTS-ACR. FRAX 10-year MOF medium or high-risk categories compared to low-risk were not significantly associated with the outcomes both in RA and OA patients. Factors associated with OPTS and OPTS-ACR in OA patients are shown in Table 4.

In sensitivity analysis, predictors for BMD testing and OP treatment were similar but being male, having no insurance, residing in a rural area, and receiving any bDMARD (vs. MTX) were more significantly associated with BMD testing than receipt of OP medications (Table 5). The predictors for OPTS and OPTS-ACR in GC-exposed RA patients of postmenopausal women and men age ≥50 years were similar that older age, longer GC duration (particularly >12 months), bDMARDs, prior fragility fracture or diagnosis of OP were associated with better OP care (Table S3).

DISCUSSION

In this large US-wide observational study, we showed that about half of the RA patients were potential candidates for OP treatment by the 2010 ACR GIOP or 2014 NOF guidelines. However, only about half of these patients ever received an OP medication. Despite being at higher risk for OP and fracture, RA patients were not more likely to be treated or screened for OP compared to OA patients after accounting for differences in sociodemographic features, BMI, GC treatment, functional disability, and FRAX 10-year MOF risk categories. Besides this suboptimal OP care, we also showed that the relative risk of undergoing OP treatment or BMD screening has been decreasing since 2008 in RA and OA patients.

Low rates of screening and preventive/therapeutic care for OP in RA patients have been reported previously (29, 30). However, OP treatment and screening trends and frequencies in accordance with the 2010 ACR GIOP and the 2014 NOF guidelines in RA patients compared to OA patients have not been examined before. Despite the importance of implementing GIOP guideline recommendations, our findings suggest that focusing only on GC-receiving RA patients would overlook nearly 1 of every 5 patients not treated with GC also deemed high-risk and for whom OP treatment would be indicated based on the 2014 NOF guideline.

Although RA patients were not examined separately, the only study estimating the proportion of GC-users who would meet the 2010 ACR GIOP guideline criteria for OP treatment showed that treatment would be recommended in over 50% of this population

(16). However, less than 30% of these patients reported treatment with bisphosphonates (alendronate and risedronate only) (16). Earlier studies including either GC-using or all RA patients also reported frequencies of 13–43% for OP treatment receipt and 23–56% for BMD testing (29–32). A few studies assessing FRAX scores showed OP treatment frequencies of 58–63% in high-risk RA patients (32, 33), which were similar to that of our high-risk RA cohort (65%). The reported treatment rates in the US general population with high fracture risk or prior fragility fracture were relatively lower (~30%) (34, 35). However, receipt of ACR-recommended OP medications and non-HRT OP medications which include the majority of the 2017 ACR GIOP guideline recommended medications (oral/parenteral bisphosphonates, teriparatide, denosumab, and raloxifene) (36) were less than 50% in RA patients. Notably, regardless of OP medication type, we could not show a better OP treatment or screening pattern in RA patients compared to patients with a non-inflammatory rheumatic disease from the same observational cohort.

Interestingly, we also observed that OP treatment and screening trends have been decreasing significantly since 2008 compared to 2003 both in RA and OA patients without meaningful changes following the release of the 2010 ACR GIOP guideline. Previous studies examining temporal trends of OP treatment or screening patterns as % changes in prevalent or incident long-term (defined as either ≥3 months or ≥6 months) GC-users reported an improvement in GIOP care rates over time compared to rates in late 1990s or early 2000s (37–40). Although these studies included RA patients, they differed from our study in terms of population type (administrative/pharmacy databases), outcomes (medication types), periods-examined (1996–2001, 2001–2003, 2001–2005 and 1998–2008), included covariates, and lastly lack of a control group (non-inflammatory patients or corresponding GC-nonusers). Nevertheless, even the improved rates for BMD testing (19%) or treatment with any OP medication (54%) were low (37–40). This suboptimal and decreasing trend for OP treatment and screening in RA patients is important as the prevalence of OP leading to fractures in RA, regardless of GC use, is still high despite aggressive management strategies and the use of bDMARDs (19). The reasons for the suboptimal and downward trend are not fully known, but data from the GIOP care improvement trials suggested both patient (lack of knowledge, unwillingness to take additional drugs, cost) and clinician (lack of experience and time, focusing more on disease activity and other comorbid conditions) barriers play a role (41).

Considering the time point of decline in OP care, certain emerged changes might have influenced both patients' and physicians' willingness to pursue OP care: Medicare reimbursement cuts for dual-energy X-ray absorptiometry (DXA) (2007), warning for jaw osteonecrosis (2006) with bisphosphonates by the US Food and Drug Administration, publications about atrial fibrillation (2007) and atypical femoral fractures associated with long-term bisphosphonate treatment (2010), and negative critical media reports about these issues (42, 43). Despite the absence of direct evidence for the effects of these factors on OP care, an increase in the internet search for alendronate and a decline in OP screening and treatment from 2008 through 2012 were reported in the US adult population (42, 44). Additionally, a survey study conducted among US physicians reported that DXA reimbursement cuts adversely influenced their DXA testing, training, and upgrading the software and consequently the prescription of OP medications (45). Atypical femoral fractures associated with long-term bisphosphonate use also might have led physicians or

patients to apply drug holidays (46). The consequences of this decline in OP care is worrying considering the plateau observed in hip fracture reduction rates for the last 3 years (47). These barriers need to be resolved more vigilantly since neither the published results from previous randomized interventional trials (41) nor the 2010 ACR GIOP guideline appear to have improved OP care in RA patients.

Several factors including older age, female gender and postmenopausal state, prior OP diagnosis or fragility fracture, and GC-use irrespective of the duration and dose were identified as strong predictors of OP care in RA patients in this study as shown previously (29, 31, 32). The factors indicating accessibility to and utilization of health care like higher education level, having insurance, urban residency, and vaccination for influenza were also associated with better OP care. Although it has been shown that higher BMI or weight was associated with a lower likelihood of developing osteoporotic fractures in RA patients (9, 19), the limited data indicates no association between BMI and BMD testing (48). We found that overweight/obese RA patients compared to normal-weight were less likely to be treated or screened for OP. This may suggest physicians' awareness of the protective effect of higher BMI for OP/fracture, but OP care in higher-risk underweight RA patients still needs to be improved.

Another factor that to our knowledge has not been examined as a potential determinant of OP care is the use of biologic treatments for RA. We found that RA patients treated with any bDMARDs were more likely to be tested with BMD, but not treated for OP. These patients might have higher disease activities and more GC-exposure prior to bDMARDs, which may explain the better screening. However, it is unknown whether the observed OP treatment patterns were due to better bone densities with better disease control or other provider concerns about bDMARDs in the clinical practice such as infections or malignancies.

There are limitations to our study. First, as the NDB mainly recruits volunteer patients or physicians, the study population is subject to participation bias, and may not be generalizable to all RA patients. However, despite the participation of more educated and disease-concerned patients, the results were suggestive of suboptimal OP care in RA patients, especially when compared to OA patients from the same cohort. Fractures and the level of trauma for those were self-reported, thus there may be some misclassification in fractures. BMD is not mandatory for the FRAX calculation, and it has been shown that FRAX without BMD is able to stratify fracture risk and may be sufficient for clinical decision making particularly in low or high-risk patients (49). Therefore, estimates referent to the frequency of OP treatment candidates might be even higher since BMD results are more likely to change fracture risk category from medium to high-risk and would allow us to use T-score of ≤-2.5 as a treatment indication. It should also be noted that the 2010 ACR GIOP guideline did not cover certain GC-using risk and age groups. Although the new 2017 ACR GIOP guideline has extended the risk groups, it should be remembered that the NOF guideline is applicable to all fracture risk groups other than GIOP and can be used in RA patients particularly in GC-nonusers. In addition to WHO FRAX, ACR GIOP or T-score-based fracture risk assessments, history of femoral neck or intertrochanteric and vertebral compression fractures (highest risk group), and expanded clinical definition of OP (50) (low-trauma clinical vertebral, proximal humerus fracture, or pelvis fracture in postmenopausal

women or men age ≥50 years with low bone density [T-score −1.0 to −2.5], or postmenopausal women with low-trauma distal forearm fracture and low bone density) should be evaluated when assessing for fracture risk.

In conclusion, ~50% of RA patients were at sufficient risk for fracture to warrant OP treatment either by ACR GIOP or NOF guidelines, but half of these patients were never treated appropriately. In addition to having suboptimal and non-superior OP care compared to OA patients, the relative risk of being treated or screened for OP in RA patients has been decreasing since 2008 compared to early 2000s. Clarification of patient and provider-related factors for suboptimal management are needed to develop effective interventions and reduce the burden of osteoporotic fractures. Considering the increased OP and fracture risk in RA patients regardless of GC use, development of an RA-specific OP prevention and management guideline might be helpful in covering all high-risk groups, optimizing the OP care and decreasing the health impact of OP complications in RA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE and INNOVATIONS

- This large US-wide observational study is the first to examine the proportion of rheumatoid arthritis (RA) patients who require osteoporosis (OP) treatment according to the 2010 ACR glucocorticoid-induced osteoporosis and 2014 National Osteoporosis Foundation management guidelines.
- About half of the RA patients were estimated to be at risk for fracture to warrant OP by both of the guidelines, but less than half ever received any OP treatment.
- OP practices in RA patients were not better compared to OA patients after accounting for differences in baseline fracture risk factors and the relative risk of undergoing OP treatment or screening has been decreasing since 2008 both in RA and OA patients.

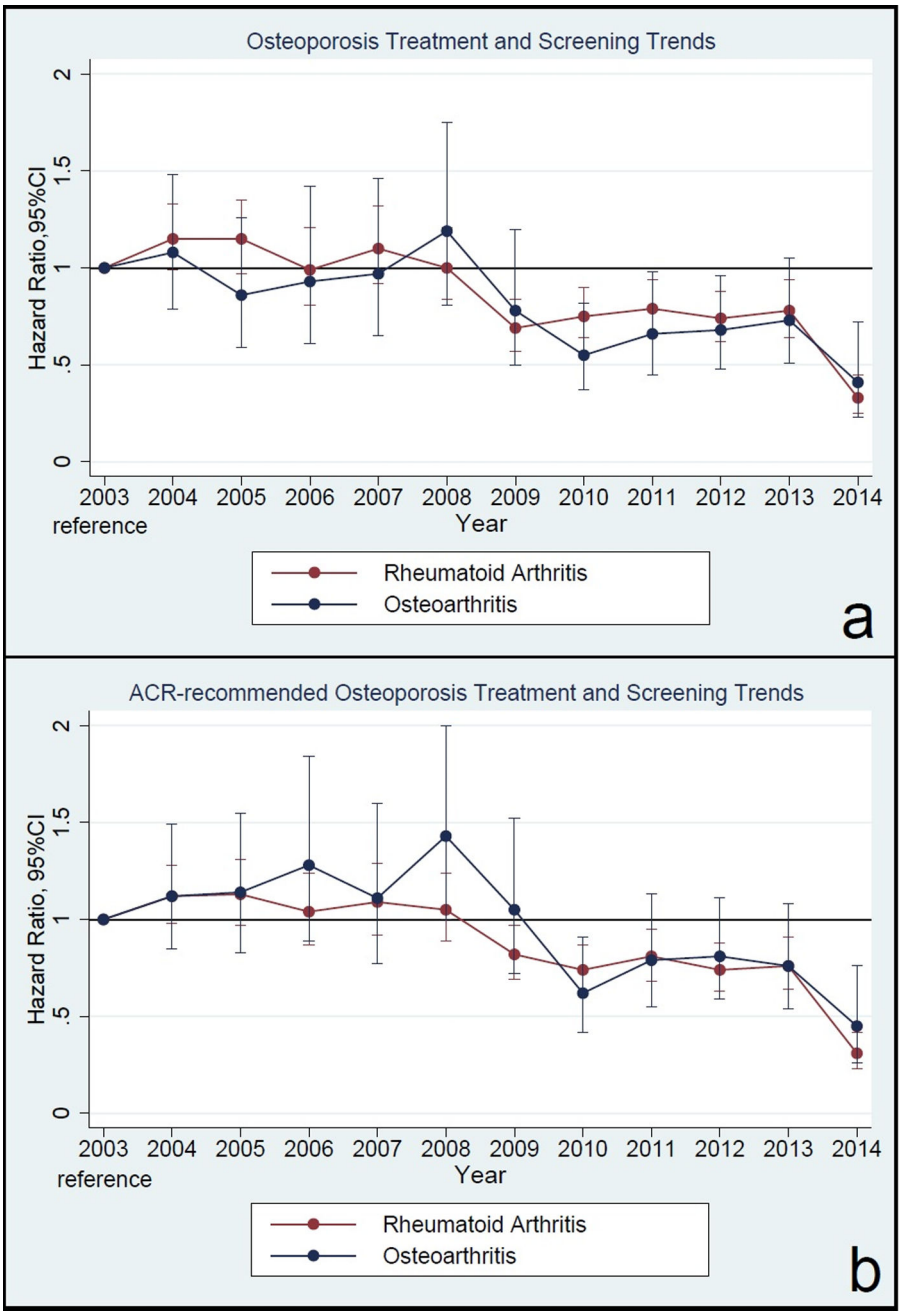

Figure 1.

Trends over time in patients with rheumatoid arthritis and osteoarthritis

a) Osteoporosis treatment and screening (any osteoporosis treatment or BMD testing)

b) ACR-recommended osteoporosis treatment and screening

Table 1

Baseline characteristics of patients with rheumatoid arthritis and osteoarthritis*

	RA Patients (N = 11,669)	OA Patients (N = 2,829)	*P* value
Age, years	59.3 ± 13.1	65.8 ± 11.2	<0.001
Age distribution, %			<0.001
<40 years	8.1	1.5	
40–50 years	14.8	6.4	
51–64 years	42.2	38.5	
≥65 years	34.9	53.6	
Women, %	80.4	82.6	0.007
Postmenopausal, %	66.6	77.9	<0.001
Men age≥50 years, %	17.1	16.4	<0.001
Non-Hispanic Caucasians, %	92.9	95.2	<0.001
Education level, years	13.9 ± 2.3	14.2 ± 2.3	<0.001
Disease duration, years	15.1 ± 12.4	16.7 ± 13.1	<0.001
HAQ (0–3)	1.1 ± 0.7	1.0 ± 0.7	0.219
BMI, kg/m^2	28.4 ± 6.8	29.7 ± 7.1	<0.001
Rheumatic Disease Comorbidity Index (0–9)	1.7 ± 1.6	1.9 ± 1.5	<0.001
Ever-smoked, %	44.8	38.6	<0.001
MTX-ever, %	72.5	-	-
Any TNFi-ever, %	41.2	-	-
Any non-TNFi bDMARDs-ever, %	7.4	-	-
Glucocorticoid-ever used	66.3	25.7	<0.001
Patterns of prednisone use, %			
Duration, median (IQR) months	21.0 (6.0–72.0)	3.0 (1.0–16.0)	<0.001
Dosage, median (IQR) mg/day	5.0 (5.0–10.0)	5.0 (5.0–10.0)	0.921
Cumulative dose, median (IQR) g	4.5 (1.2–12.4)	0.9 (0.3–7.5)	<0.001
10-year MOF risk by FRAX, median (IQR) %	10.5 (5.5–18.7)	10.5 (6.2–17.8)	0.364
10-year MOF risk categories by FRAX, %			<0.001
Low (<10%)	47.8	47.4	
Medium (10–20%)	29.7	32.9	
High (>20%)	22.4	19.7	
10-year hip fracture risk by FRAX (%), median (IQR) %	1.6 (0.5–5.1)	1.9 (0.6–5.2)	0.002
Hip fracture risk categories by FRAX, %			0.006
Low-Medium (<3%)	63.8	61.9	
High (≥3%)	36.2	38.1	
Prior fragility fracture, %	29.7	28.9	0.397
Prior diagnosis of osteoporosis, %	25.4	27.4	0.026
Age at osteoporosis diagnosis, years	61.9 ± 11.7	66.4 ±10.9	<0.001

	RA Patients (N = 11,669)	OA Patients (N = 2,829)	*P* value
BMD testing, %	21.2	21.3	0.958
Calcium and/or Vitamin D supplementation, %	43.6	45.5	0.055
OP specific medications, %	31.4	31.0	0.665
Bisphosphonates	16.9	13.2	<0.001
Hormone replacement therapy	15.8	17.4	0.006
Raloxifene	2.3	3.5	<0.001
Teriparatide	0.01	0.01	0.826

*The values are presented as mean± SD unless indicated otherwise.

RA= Rheumatoid arthritis; OA= Osteoarthritis; HAQ= Health assessment questionnaire; BMI= Body mass index; MTX= Methotrexate; TNFi= Tumor necrosis factor-α inhibitors; bDMARDs= Biologic disease modifying antirheumatic drugs; IQR=Interquartile range; FRAX= Fracture risk assessment tool; OP= Osteoporosis; BMD=Bone mineral densitometry.

Table 2

Crude incidence rates for osteoporosis treatment and screening in patients with rheumatoid arthritis and osteoarthritis*

	Entire cohort		Patients without BMD testing or any OP treatment at baseline	
	RA patients, N=11,669	**OA patients, N=2,829**	**RA patients, N=6,611**	**OA patients, N=1,617**
Follow-up, median (IQR) years	5.5 (2.3–9.0)	5.5 (2.1–9.1)	5.1 (2.0–8.7)	5.3 (1.8–8.9)
OP treatment and/or screening (OPTS)				
Total events, %	67.4	64.6	42.5	38.0
Person-years	22,116	5,225	19,577	4,619
Incidence rate (95% CI) per 100 person-years	35.6 (34.8–36.4)	34.9 (33.4–36.6)	14.3 (13.8–14.9)	13.3 (12.3–14.4)
ACR-recommended OP-treatment and/or screening (OPTS-ACR)				
Total events, %	61.8	56.7	39.6	34.6
Person-years	25,601	6,362	12,563	2,891
Incidence rate (95% CI) per 100 person-years	28.2 (27.5–28.8)	25.2 (24.0–26.5)	12.9 (12.5–13.5)	11.7 (10.7–12.7)

*Anti-OP treatment does not include calcium and/or vitamin D supplementation.

OP=Osteoporosis; RA= Rheumatoid arthritis; OA= Osteoarthritis; IQR=Interquartile range; OPTS=Osteoporosis treatment and screening; ACR= American College of Rheumatology; OPTS-ACR=ACR-recommended OP treatment and screening

Table 3

Calcium/vitamin D supplementation, BMD testing, and osteoporosis treatment frequencies in patients with rheumatoid arthritis and osteoarthritis in the entire follow-up

	RA patients	OA patients	*P* value
All patients, N	**11,669**	**2,829**	
Calcium and/or vitamin D supplementation, %	63.9	66.4	<0.001
BMD testing, %	57.8	54.1	<0.001
Any OP treatment, %	44.0	42.1	0.063
Any ACR recommended OP treatment	26.4	21.2	<0.001
Any OP treatment excluding HRT	30.1	25.3	<0.001
Postmenopausal women and men age≥50 years who ever exposed to GC, N (%)	**7,434 (63.7)**	**894 (31.6)**	
Calcium and/or vitamin D supplementation, %	69.8	73.1	0.038
BMD testing, %	65.4	62.2	0.058
Any OP treatment, %	50.5	47.5	0.093
Any ACR recommended OP treatment, %	32.3	24.5	<0.001
Any OP treatment excluding HRT	36.4	29.2	<0.001
High-risk patients by 10-year MOF FRAX score, N (%)	**2,619 (22.4)**	**557 (19.7)**	
Calcium and/or vitamin D supplementation, %	80.4	82.2	0.324
BMD testing, %	73.7	68.2	0.008
Any OP treatment, %	65.6	62.8	0.221
Any ACR recommended OP treatment	49.6	42.6	0.002
Any OP treatment excluding HRT	54.9	49.6	0.020
OP treatment candidates by the 2010 ACR GIOP guideline, N (%)	**5,646 (48.4)**	**497 (17.6)**	
Calcium/vitamin D supplementation, %	71.8	77.4	0.013
BMD testing, %	69.3	70.4	0.106
Any OP treatment, %	54.9	55.5	0.845
Any ACR-recommended OP treatment, %	37.4	38.4	0.006
Any OP treatment excluding HRT	41.8	39.6	0.021
OP treatment candidates by the 2014 NOF guideline, N (%)	**5,748 (49.3)**	**1,455 (51.4)**	
Calcium and/or vitamin D supplementation, %	71.9	72.5	0.646
BMD testing, %	66.7	62.1	<0.001
Any OP treatment, %	54.5	49.8	<0.001
Any ACR recommended OP treatment, %	37.7	29.9	<0.001
Any OP treatment excluding HRT	42.5	35.7	<0.001

RA= Rheumatoid arthritis; OA= Osteoarthritis; BMD=Bone mineral densitometry; OP=Osteoporosis; ACR= American College of Rheumatology; HRT= Hormone replacement therapy; GC=Glucocorticoid; MOF= Major osteoporotic fracture; FRAX= Fracture risk assessment tool; GIOP=Glucocorticoid induced osteoporosis; NOF= National Osteoporosis Foundation.

Table 4

Predictors for both type of osteoporosis treatment and screening in patients with rheumatoid arthritis and osteoarthritis

Variables	OPTS, HR (95% CI)		OPTS-ACR, HR (95% CI)	
	RA patients	OA patients	RA patients	OA patients
Age groups				
<40 years (referent)	1.0	1.0	1.0	1.0
40–50 years	1.70 (1.38–2.10)	1.99 (0.68–5.82)	2.07 (1.65–2.59)	1.68 (0.49–5.74)
51–64 years	2.25 (1.80–2. 81)	2.19 (0.74–6.51)	2.98 (2.35–3.77)	3.23 (0.94–11.05)
≥65 years	2.77 (2.17–3.55)	2.22 (0.73–6.73)	3.82 (2.96–4.95)	3.54 (1.02–12.28)
Gender				
Women				
Premenopausal (referent)	1.0	1.0	1.0	1.0
Postmenopausal	1.64 (1.39–1.94)	2.51 (1.41–4.48)	1.57 (1.33–1.84)	1.67 (0.93–3.02)
Men	0.56 (0.46–0.67)	0.58 (0.31–1.08)	0.51 (0.42–0.61)	0.41 (0.21–0.77)
Education level	1.03 (1.01–1.05)	1.05 (1.01–1.09)	1.03 (1.01–1.04)	1.03 (0.99–1.06)
No insurance	0.66 (0.51–0.87)	0.97 (0.54–1.74)	0.57 (0.44–0.75)	0.32 (0.14–0.72)
Residency in a rural area	0.88 (0.81–0.95)	0.90 (0.74–1.09)	0.90 (0.83–0.97)	0.91 (0.77–1.08)
Disease duration	1.00 (0.99–1.00)	1.00 (0.99–1.01)	1.00 (0.99–1.00)	1.00 (0.99–1.00)
Vaccination for influenza	1.13 (1.05–1.23)	1.23 (1.03–1.45)	1.13 (1.05–1.21)	1.12 (0.97–1.30)
Rheumatic Disease Comorbidity Index	1.05 (0.99–1.10)	1.01 (0.92–1. 11)	1.02 (0.97–1.06)	1.03 (0.95–1.12)
BMI in categories				
<18.5 kg/m2	1.01 (0.76–1.34)	0.83 (0.26–2.64)	1.12 (0.88–1.42)	0.24 (0.03–1.75)
18.5–24.9 kg/m2 (referent)	1.0	1.0	1.0	1.0

Variables	OPTS, HR (95% CI)		OPTS-ACR, HR (95% CI)	
	RA patients	OA patients	RA patients	OA patients
25.0–29.9 kg/m2	0.85 (0.78–0.94)	0.78 (0.63–0.96)	0.88 (0.81–0.96)	0.83 (0.69–1.00)
30.0–39.9 kg/m2	0.76 (0.69–0.85)	0.62 (0.50–0.78)	0.84 (0.76–0.92)	0.68 (0.55–0.82)
≥40 kg/m2	0.52 (0.44–0.63)	0.50 (0.36–0.70)	0.57 (0.49–0.67)	0.53 (0.39–0.72)
HAQ	1.06 (0.99–1.12)	0.91 (0.81–1.03)	1.02 (0.97–1.07)	0.94 (0.85–1.05)
Glucocorticoid use				
Not-using (referent)	1.0	1.0	1.0	1.0
<3 months	1.34 (1.12–1.60)	0.99 (0.56–1.76)	1.34 (1.13–1.57)	1.14 (0.72–1.33)
3–12 months	1.36 (1.18–1.57)	1.67 (0.96–2.89)	1.41 (1.24–1.61)	1.24 (0.72–2.13)
>12 months	1.66 (1.49–1.83)	1.84 (1.05–3.22)	1.63 (1.49–1.78)	1.75 (1.09–2.82)
Use of DMARDs				
MTX monotherapy (referent)	1.0	-	1.0	-
Any TNFi	1.22 (1.09–1.37)	-	1.79 (1.07–1.30)	-
Non-TNFi bDMARDs	1.38 (1.12–1.69)	-	1.30 (1.07–1.57)	-
Any others	1.15 (1.03–1.28)	-	1.08 (0.98–1.19)	-
Prior fragility fracture	1.17 (1.05–1.31)	1.31 (1.03–1.66)	1.20 (1.09–1.33)	1.35 (1.10–1.65)
Prior diagnosis of OP	1.52 (1.31–1.76)	1.52 (1.13–2.05)	1.49 (1.30–1. 71)	1.50 (1.14–1.96)
10-year major osteoporotic fracture risk categories by FRAX				
Low (referent)	1.0	1.0	1.0	1.0
Medium	0.98 (0.88–1.10)	0.98 (0.78–1.23)	1.01 (0.92–1.12)	0.98 (0.80–1.21)

Variables	OPTS, HR (95% CI)		OPTS-ACR, HR (95% CI)	
	RA patients	OA patients	RA patients	OA patients
High	0.86 (0.74–1.01)	0.82 (0.59–1.13)	0.87 (0.76–1.01)	0.84 (0.62–1.12)

OPTS=Osteoporosis treatment and screening; OPTS-ACR=ACR-recommended OP treatment and screening; ACR= American College of Rheumatology; HR=Hazard ratio; RA= Rheumatoid arthritis; OA= Osteoarthritis; BMI= Body mass index; HAQ= Health assessment questionnaire; DMARD= Disease modifying antirheumatic drug; MTX=Methotrexate; TNFi= Tumor necrosis factor-α inhibitor; bDMARDs= Biologic disease modifying antirheumatic drugs; OP= Osteoporosis; FRAX= Fracture risk assessment tool.

Table 5

Predictors of osteoporosis treatment and BMD testing as separate outcomes in patients with rheumatoid arthritis

Variables	OP treatment, HR (95% CI)	ACR recommended OP treatment, HR (95% CI)	OP treatment excluding HRT, HR (95%CI)	BMD testing, HR (95% CI)
Age groups				
<40 years (referent)	1.0	1.0	1.0	1.0
40–50 years	1.31 (0.97–1.77)	1.74 (1.04–2.94)	1.99 (1.21–3.28)	2.10 (1.69–2.62)
51–64 years	1.47 (1.06–2.03)	2.45 (1.43–4.21)	2.88 (1.71–4.84)	2.96 (2.35–3.74)
≥65 years	1.54 (1.07–2.19)	3.44 (1.96–6.05)	4.08 (2.37–7.00)	3.53 (2.76–4.52)
Gender				
Women				
Premenopausal (referent)	1.0	1.0	1.0	1.0
Postmenopausal	1.86 (1.45–2.38)	1.61 (1.11–2.33)	1.66 (1.18–2.34)	1.56 (1.33–1.83)
Men	0.77 (0.58–1.01)	0.85 (0.57–1.27)	0.75 (0.52–1.09)	0.54 (0.46–0.65)
Education level	1.02 (0.99–1.05)	1.00 (0.98–1.03)	1.01 (0.99–1.04)	1.03 (1.01–1.04)
No insurance	0.88 (0.61–1.28)	0.90 (0.55–1.49)	0.83 (0.51–1.36)	0.51 (0.39–0.67)
Residency in a rural area	0.98 (0.88–1.10)	1.03 (0.91–1.16)	1.00 (0.89–1.13)	0.88 (0.83–0.95)
Disease duration	1.00 (0.99–1.00)	1.00 (1.00–1.01)	1.00 (1.00–1.01)	1.00 (0.99–1.00)
Vaccination for influenza	1.15 (1.03–1.28)	1.11 (0.98–1.25)	1.14 (1.02–1.28)	1.13 (1.06–1.20)
Rheumatic Disease Comorbidity Index	1.09 (1.03–1.15)	1.01 (0.96–1.08)	1.03 (0.97–1.09)	0.99 (0.96–1.04)
BMI in categories				
<18.5 kg/m2	1.10 (0.76–1.58)	1.47 (1.05–2.05)	1.35 (0.97–1.88)	1.08 (0.87–1.33)
18.5–24.9 kg/m2 (referent)	1.0	1.0	1.0	1.0

Variables	OP treatment, HR (95% CI)	ACR recommended OP treatment, HR (95% CI)	OP treatment excluding HRT, HR (95%CI)	BMD testing, HR (95% CI)
25.0–29.9 kg/m2	0.66 (0.59–0.76)	0.61 (0.53–0.70)	0.64 (0.56–0.73)	0.89 (0.83–0.96)
30.0–39.9 kg/m2	0.58 (0.50–0.66)	0.59 (0.51–0.69)	0.57 (0.49–0.66)	0.85 (0.78–0.92)
≥40 kg/m2	0.40 (0.30–0.52)	0.46 (0.34–0.63)	0.42 (0.31–0.56)	0.64 (0.55–0.74)
HAQ	1.08 (0.99–1.16)	0.98 (0.96–1.09)	1.01 (0.93–1.10)	0.99 (0.95–1.03)
Glucocorticoid use				
Not-using (referent)	1.0	1.0	1.0	1.0
<3 months	1.32 (1.02–1.72)	1.45 (1.06–1.98)	1.43 (1.06–1.92)	1.22 (1.04–1.43)
3–12 months	1.30 (1.06–1.59)	1.70 (1.35–2.13)	1.70 (1.37–2.11)	1.33 (1.18–1.50)
>12 months	1.66 (1.46–1.90)	1.93 (1.68–2.22)	1.94 (1.70–2.22)	1.48 (1.37–1.60)
Use of DMARDs				
MTX monotherapy (referent)	1.0	1.0	1.0	1.0
Any TNFi	1.16 (0.99–1.36)	1.01 (0.86–1.20)	1.06 (0.90–1.25)	1.15 (1.06–1.26)
Non-TNFi bDMARDs	1.29 (0.97–1.71)	1.24 (0.90–1.71)	1.31 (0.97–1.77)	1.21 (1.01–1.45)
Any others	1.11 (0.95–1.29)	0.90 (0.77–1.06)	0.94 (0.81–1.10)	1.07 (0.98–1.16)
Prior fragility fracture	1.35 (1.17–1.56)	1.61 (1.37–1.88)	1.55 (1.33–1.81)	1.21 (1.11–1.32)
Prior diagnosis of OP	1.58 (1.29–1.93)	2.25 (1. 78–2.85)	2.28 (1.83–2.85)	1.38 (1.23–1.55)
10-year major osteoporotic fracture risk categories by FRAX				
Low (referent)	1.0	1.0	1.0	1.0
Medium	0.98 (0.84–1.15)	1.10 (0.92–1.32)	1.07 (0.90–1.27)	1.09 (0.99–1.20)
High	1.07 (0.86–1.32)	01.16 (0. 91–1.48)	1.07 (0.85–1.34)	0.96 (0.84–1.09)

OPTS=Osteoporosis treatment and screening; OPTS-ACR=ACR-recommended OP treatment and screening; ACR= American College of Rheumatology; HR=Hazard ratio; HRT= Hormone replacement therapy; RA= Rheumatoid arthritis; OA= Osteoarthritis; BMI= Body mass index; HAQ= Health assessment questionnaire; DMARD= Disease modifying antirheumatic drug; MTX=Methotrexate; TNFi= Tumor necrosis factor-α inhibitor; bDMARDs= Biologic disease modifying antirheumatic drugs; OP= Osteoporosis; FRAX= Fracture risk assessment tool.