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Sex Differences in the Achievement of Remission and Low Disease Activity in Rheumatoid Arthritis

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Abstract

Objective
In rheumatoid arthritis (RA), it is unclear if women are less likely to achieve low disease activity (LDA). We evaluated sex differences in remission and LDA, comparing different clinical and imaging measures.

Methods
We utilized data from the Veterans Affairs RA (VARA) registry and from two clinical trials. Remission and LDA were defined using composite scores, individual items (tender joints, swollen joints, ESR, CRP, evaluator/patient global assessment), and MRI. In VARA, we assessed 1) the likelihood of point remission at any time during follow-up using logistic regression, and 2) time to sustained remission (2 consecutive visits) using Cox proportional hazard models. In the clinical trials, logistic regression models evaluated the likelihood of low clinical and MRI activity at 52 weeks.

Results
Among 2463 patients in VARA women (10.2%) were less likely to be in DAS28-ESR remission in follow-up [OR: 0.71 (0.55, 0.91) p<0.01] and had a longer time to sustained DAS28-ESR remission. This difference was not observed for DAS28-CRP, CDAI, or RAPID3. Women were more likely to achieve favorable individual components except for an ESR <30 mm/hr [OR: 0.72 (0.57, 0.90) p<0.01]. Among 353 trial participants, (83.7% women), women had reduced rates of DAS28-ESR remission [OR: 0.39 (0.21, 0.72) p=0.003] but similar rates of low MRI synovitis and osteitis.

Conclusion
The comparison of remission rates between men and women varies based on the disease activity measure, with sex-specific differences in ESR resulting in reliably lower rates of remission among women. There were no differences in MRI-measures.

Key Words: Sex; Rheumatoid Arthritis; Remission; Disease Activity

Significance and Innovations

1. In this study of two large rheumatoid arthritis (RA) cohorts, women were consistently less likely to achieve low ESR levels and DAS28-ESR remission.
2. There were not consistent sex differences in remission or low disease activity for other composite RA disease activity measures.
3. Achievement of low synovitis and osteitis scores on MRI of the hand and wrist were similar between men and women.
4. Sex-specific thresholds to define DAS28-ESR remission and low disease activity may be of value.

There are epidemiological differences between men and women with rheumatoid arthritis (RA) with women having a higher prevalence, younger age at onset, and lower frequency of seropositivity (1–3). It has also been noted that women with RA are less likely than men to achieve clinical remission (2,4–6). However, these sex differences remain incompletely understood.

The American College of Rheumatology (ACR) encourages the use of a disease activity measure in patients with RA and several composite measures of disease activity have been recommended for clinical use and endorsed as quality measures (7). A recent nationwide survey of US rheumatologists found that the most used outcome measures (functional status and disease activity) in the care of RA patients are the Health Assessment Questionnaire (HAQ) or Multi-Dimensional (MD)-HAQ (35.5%), Routine Assessment of Patient Index Data (RAPID3) (27.1%), Clinical Disease Activity Index (CDAI) (17.5%) and the Disease Activity Score of 28 joints (DAS28) (15.7%) (8). While a number of disease activity measures are utilized, studies have demonstrated that the rate of remission depends significantly on the criteria used (4,9–13).

Previous studies evaluated differences in component and composite measures of disease activity specifically in men and women with RA and suggested that remission rates for women are anywhere from 30% to 87% percent lower (10). Multiple studies using the QUEST-RA registry, a cross sectional international registry study, showed that women were less likely to achieve remission defined by DAS28 with Erythrocyte Sedimentation Rate (DAS28-ESR) as well by the CDAI and RAPID3 (14). A study in Finland found that women were less likely to be in DAS28-ESR remission at baseline, 2 years, and 5 years, but there was no difference between sexes when considering Boolean remission (4). In a study from the Corrona RA registry, a large prospective cohort study, women were less likely to achieve CDAI early sustained remission (5), however, there was no difference in established remission or in early point remission. Another recent study noted that women were less likely to achieve remission

when defined by DAS28-ESR, CDAI, and Simple Disease Activity Index (SDAI) but found no difference in remission rates for Boolean criteria or RAPID3 (9). Overall, these studies suggest a more refractory phenotype among women, but the results lack consistency and vary based on the composite outcomes utilized and population studied.

Observed differences in remission rates between men and women may be the result of differences in the accuracy of disease activity measures in these two groups. For example, in other settings the ESR is known to be higher in women (15). Laboratories using the Westergren method have reference ranges for ESR that vary by age and sex (16). While the ACR remission criteria defines inactive ESR differently for female and male patients (17,18), the DAS28-ESR does not take into account this difference in ESR values between sexes (15,18). This leads to higher DAS28-ESR values compared to the DAS28 with C-Reactive Protein (DAS28-CRP) in older women (19). CRP can be also be falsely elevated in obese women with RA; a bias that is less apparent among men (20). Additionally, women have been shown to report higher pain scores compared to men in the general population, suggesting that subjective assessments may be influenced by differences in reporting (21,22). For these reasons, the lack of a direct measure of joint inflammation is a major limitation in prior studies. We are aware of no prior studies that compared men and women in the achievement of low activity based on imaging criteria. Recently, a definition of low MRI activity has been defined (23,24).

We aimed to compare the rates of remission and low disease activity between men and women using different composite and component measures, hypothesizing that sex differences in attainment of remission and low disease activity would vary depending on the measurement tool used. Furthermore, we hypothesized that achievement of low MRI activity would be similar in between men and women.

Methods

Study Setting

Veterans Affairs Rheumatoid Arthritis Registry Study

This is an analysis of a prospective cohort study of US veterans with RA using the Veterans Affairs Rheumatoid Arthritis (VARA) registry of patients enrolled between January 2003 and 2016. The VARA registry is a multicenter (12 active US sites) biorepository and longitudinal observational study of US veterans with RA. All participants satisfy the ACR classification criteria for RA and disease onset after 18 years of age. Detailed clinical and laboratory data are collected at baseline and at subsequent rheumatology clinic visits. Eligible patients are systematically enrolled from participating rheumatology clinics with RA patient characteristics that are reflective of the national VA population. Regulatory approval was obtained, and studies were approved by the IRB at each individual site.

GO-BEFORE and GO-FORWARD Clinical Trials

The study population comes from secondary analysis of the GO-BEFORE (Clinicaltrials.gov identifier NCT00361335) and GO-FORWARD (NCT00264550) randomized, multicenter, double-blind, placebo-controlled trials which evaluated the efficacy of tumor necrosis factor alpha (TNF-α) antagonist golimumab for the treatment of RA. Both studies compared golimumab in combination with methotrexate to methotrexate or golimumab monotherapy. Detailed methods and results of both studies have previously been published (25,26). The trials were conducted according to the Declaration of Helsinki. Secondary analysis of de-identified trial data was considered exempt by the Internal Review Board at the University of Pennsylvania.

This analysis includes the subset of patients in both studies who had MRIs scored for synovitis, osteitis, and/or bone erosion at baseline and at 52-weeks of follow-up (the original follow-up duration for the trial). Patients ≥18 years old who met ACR 1987 criteria for RA and had active disease were recruited into the MRI sub-study at participating sites. Data collection through 52 weeks included blinded assessments of disease activity. MRI was performed at baseline and week 52. MRIs of the dominant wrist and 2^{nd}-5^{th} metacarpophalangeal (MCP)

joints were obtained using a 1.5T MRI with contrast enhancement as previously described and scored by two independent blinded readers using the RAMRIS scoring system (27).

Definitions of Remission and Low Disease Activity

We compared the achievement of remission and low disease activity between men and women as defined by several common composite scores: 1) DAS28-ESR, 2) DAS28-CRP, 3) CDAI, and 4) RAPID3. These disease activity scores were chosen based on a combination of composite indices, with and without acute phase reactants, patient reported instruments, commonly used in clinical trials, and recommended by ACR/EULAR 2011 for use in clinical practice (7). Remission and low disease activity were defined based on previously published thresholds for each composite score (28).

We also compared the achievement of individual low component measures defined based on ACR/EULAR 2011 recommendations, Boolean criteria and other prior published guidelines. Remission for component scores was defined as ESR < 30 mm/hour, CRP ≤1 mg/dL, swollen joint count (SJC28) ≤1, tender joints count (TJC28) ≤1, patient global assessment (PtGA; 0 to 10 scale) ≤1, evaluator global assessment (EvGA; 0 to 10 scale) ≤1, MD-HAQ ≤0.5, and Pain (0 to 10 scale) ≤1. Normal ESR was also defined separately based on previously described age- and sex- specific thresholds (ESR <30 mm/hour and <20 mm/hour for women and men over 50, respectively; ESR <20 mm/hour and <15 mm/hour for women and men younger than 50, respectively) (16). Low MRI synovitis and low osteitis scores were defined as a RAMRIS score ≤3 based on recently defined thresholds (27).

Covariates

ESR and CRP were extracted from the VARA registry data or medical record within 30 days of each study visit. Baseline demographics, disease duration, smoking status, and common comorbidities were extracted from the registry database. Enrollment weight and height

were extracted from medical records (within 30 days) or registry data and were converted to body mass index (BMI, kg/m^2). Covariables of interest from the clinical trial data included demographics, treatment group, and study (GO-BEFORE v. GO-FORWARD).

Statistical Analysis

For analyses in the VARA registry data, the differences in characteristics at enrollment between men and women were assessed using t-tests of significance, ranksum tests, and chi-squared tests. We evaluated achievement of remission or low disease activity in two ways: 1) point achievement among all participants over all observations and 2) the time to sustained achievement (defined as 2 consecutive visits) among those not in remission at enrollment. Statistical methods included 1) logistical models that incorporated generalized estimating equations with robust estimators to allow clustering on patient and 2) multivariable Cox proportional hazard models. To avoid adjustment for factors that might be in the causal pathway, we built parsimonious multivariable models that included factors such as age, race, disease duration, and smoking status at enrollment. Cox proportional hazards models were further adjusted for differences in biologic and prednisone use at enrollment. Visits where the component or composite measure of interest was missing were not included in the analysis.

For analyses using clinical trial data, outcomes for clinical composite and component measures as well as MRI activity measures were evaluated at 52 weeks. The percent of men and women achieving low disease activity measures by 52 weeks were determined. Multivariable logistic regression models assessed the likelihood of achieving remission by 52 weeks among men and women adjusting for age, race, study (GO-BEFORE v. GO-FORWARD), and treatment group.

Results

Rates of Remission and Low Disease Activity in the VARA Registry

The baseline characteristics of the VARA population are shown in **Table 1**. The median duration of follow-up was 2.6 years (IQR 0.85, 5.4) and the median number of visits was 21 (IQR 11, 21). Missing data in follow-up varied for composite and component measures ranging from 1% to 30% of observations. The greatest missingness was observed for the EvGl score. At enrollment, women were younger, had higher BMI, were more likely to be black, and were less likely to smoke or to have been diagnosed with chronic kidney disease, diabetes mellitus, hypertension, or chronic lung disease. Women were more likely to use biologics and less likely to use prednisone at enrollment. Women also had lower SJC28, CRP, EvGA, and MD-HAQ at baseline.

At any point in time, the adjusted odds of point remission for women were lower for DAS28-ESR [OR: 0.71 (0.55, 0.91) p<0.01] (**Table 2**). Similarly, women were less likely to have an ESR <30 mm/hour [OR: 0.72 (0.57, 0.90) p<0.01]. However, in contrast, women were more likely to achieve a low ESR when using an age-, and sex-specific definition of low ESR [OR: 1.32 (1.05, 1.64) p=0.02]. In addition, among men and women who met strict criteria for Boolean remission, women were substantially less likely to be in DAS28-ESR remission [OR: 0.42 (0.25, 0.69) p=0.001] or low disease activity [OR: 0.28 (0.088, 0.88) p=0.03]. Women were numerically but not significantly less likely to be in low disease activity based on the DAS28-ESR (**Table 2**). Adjusted rates of remission were not different for other composite scores. Women were also more likely to be in CDAI low disease activity (≤10) [OR: 1.36 (1.08, 1.73) p=0.01] and were more likely to have a low SJC28, CRP, and EvGA.

Table 3 shows that, among patients who were not in remission at enrollment, women were substantially less likely to reach DAS28-ESR sustained remission [HR: 0.53 (0.35, 0.80) p<0.01]. There was no difference in remission rates between men and women for the DAS28-CRP, CDAI, RAPID3, or achievement of sustained low disease activity (by any composite measure). Women were less likely to have achieved a sustained low ESR (<30 mm/hour) [HR: 0.50 (0.34, 0.74) p=0.001]. Women were more likely, however, to achieve low patient global

assessment (≤1) [HR: 1.49 (1.02, 2.18) p=0.04]. There was no sex difference in the likelihood of achieving low values for other individual components.

Sex Differences in Remission Rates in a Clinical Trial Setting

The clinical trial population was distinct from the VARA population in that the participants were much younger, had a lower BMI, and were more likely to be female. Men (N=58) and women (N=295) were similar in terms of age, race, and BMI. Men and women had similar DAS28-CRP and CDAI at baseline, but women had higher DAS28-ESR and higher patient global and tender joint counts (**Table 4**). Women were less likely to achieve remission by 52 weeks when remission was defined by the DAS28-ESR [OR: 0.39 (0.21, 0.72) p=0.003] (**Figure 1, Table 5**). In multivariable models, women were also less likely to achieve CDAI remission [OR: 0.50 (0.26, 0.94) p=0.03] (**Table 5**). However, there was not a significant difference in the achievement of remission between men and women for DAS28-CRP [OR: 0.71 (0.39, 1.28) p=0.26]

Among component scores, women were less likely to reach a low patient global score, were less likely to reach a low ESR (<30 mm/hr), and less likely to reach a low tender joint count (p=0.056) (**Table 5**). Women were not less likely to reach a low ESR when using an age- and sex-specific threshold [OR: 0.71 (0.39, 1.27) p=0.25]. Men and women achieved a low CRP, a low swollen joint count, and a low evaluator global score with comparable frequency. Men and women also achieved low MRI synovitis scores and osteitis scores with similar frequency.

Discussion

Our study demonstrates that comparisons between men and women with RA in the rates of achievement of clinical remission and low disease activity vary substantially by the measure used to define remission. In particular, women were consistently less likely to achieve DAS28-

ESR remission, while there was no consistent difference in remission rates or rates of low disease activity between men and women for the DAS28-CRP, CDAI, RAPID3, or for MRI measurement of synovitis or osteitis.

Several prior studies showed that women are less likely to achieve remission when using the DAS28-ESR (1,2,9,14), but there are less consistent findings in studies examining the performance of CDAI and RAPID3 (5,9,14). Our study confirmed that women are less likely to reach remission when defined by the DAS28-ESR. However, while separate analysis of the component scores revealed that women were less likely achieve a low ESR, they were actually more likely to achieve a low ESR when “low” was defined using an age- and sex-specific definition (15,16). In addition, women were more likely to achieve CDAI low disease activity in the same population. These results suggest that in the absence of accounting for sex, there is significant bias related to the inclusion of this inflammatory marker in the composite measurement of disease activity.

While other RA populations have more consistently shown that women are more likely to have higher disease activity and are less likely to achieve remission, the study of the VARA registry population suggested features of more severe disease in men. This was manifested by men having higher CRP, SJC28, and EvGA scores at enrollment and a lower likelihood of low values for these component assessments in follow-up. It is likely that these differences stem from the distinct population studied here, namely the study of veterans. While this study population is distinct from prior studies, the lack of consistency with prior findings in this population is important. It suggests that a biologic cause for sex differences in disease activity and response is less likely. Rather differences between men and women are hypothesized to reflect differences in psychosocial, economic, and other non-biologic factors that are likely to vary between populations studied.

An advance of this study over prior research is the inclusion of clinical trial data with a validated direct measure of joint inflammation, specifically MRI. While evaluation of this clinical

trial population confirmed differences between men and women in remission rates for the DAS28-ESR, CDAI, ESR, and patient global scores, there were no differences in the achievement of low MRI measures of joint inflammation. While by no means a definitive quantitation of the burden of disease, this additional evaluation provided by direct imaging assessment further suggests that previously noted sex differences may suffer from bias in clinical assessment as opposed to a true biologic difference.

There are several limitations to our study. This population of US veterans with RA does not necessarily represent the typical national RA population which is generally greater than 70% women (1). Results of this study in female veterans may not be fully generalizable to the general population. The use of a VA population may also be considered a strength, since biologic differences between men and women should be robust across populations with different psychosocial or economic backgrounds. Furthermore, patients in the VA system have relatively more equal access to care, which mitigates biases related to these issues when assessing disease outcomes. A limitation of research evaluating different disease activity assessments is that a gold standard assessment of RA disease activity does not exist. While MRI was used here as an alternative method of quantifying joint disease, it may not capture all aspects of RA disease activity. MRI does, however, provide an objective measure of inflammatory joint disease, a defining feature of RA. The use of validated cutoff scores that identify an informative degree of inflammatory disease is another strength. Our study was also limited in the ability to evaluate the reasons for the observed sex differences in ESR including differences in adiposity, hemoglobin levels, and other factors.

Other strengths of the study include the use of a large sample of well-characterized patients from two distinct RA populations with long-term follow-up. To our knowledge, this study is the first to comprehensively assess sex differences using a number of different composite and component measures of disease activity, the first to utilize age-, and sex- specific thresholds for ESR, and the first to evaluate sex-differences in the achievement of low MRI inflammation.

In conclusion, these data do not support systematic biologic differences between men and women with RA in clinical response. Furthermore, these data illustrate that comparisons in disease activity between men and women with RA should not be performed using the DAS28-ESR since rates of remission will vary based on expected differences in the inflammatory marker. In addition, studies that use the DAS28-ESR as a covariable should consider that the composite measure performs differently in men and women with RA and there may be important sex-interactions that may require stratified analyses. Finally, these observations have implications for clinicians adhering to a treat to target paradigm or assessing quality of care. Use of the DAS28-ESR may result in the over-treatment of women relative to men and may result in the inaccurate conclusion that poor quality of care is being provided to women. The future development of sex-specific definitions of clinical remission for RA using the DAS28-ESR and other composite indices may be of value.

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Conflicts of Interest

The authors have nothing to disclose.

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Tables

Table 1. Baseline characteristics in men and women from VARA.

	Men	Women	p-value
N	2211	252	
Age (years)	71.3 (9.9)	61.2 (12.7)	<0.001
Black, n (%)	307 (14%)	83 (33%)	<0.001
BMI* (kg/m^2)	28.3 (5.4)	30.1 (6.7)	<0.001
Anti-CCP positive, n (%)	1320/1670 (79%)	137/188 (73%)	0.051
Disease duration, years†	8.6 (2.5, 18.4)	6.9 (2.6, 14)	0.07
Chronic Kidney Disease, n (%)	58 (3%)	1 (0.4%)	0.03
Diabetes, n (%)	452 (20%)	33 (13%)	<0.01
Hypertension, n (%)	1191 (54%)	95 (38%)	<0.001
Osteoarthritis, n (%)	375 (17%)	31 (12%)	0.06
Depression, n (%)	177 (8%)	17 (7%)	0.81
Lung Disease, n (%)	355 (16%)	10 (4%)	<0.001
Tobacco Use, n (%)			
Current	589 (27%)	41 (17%)	<0.001
Former	1217 (56%)	84 (35%)	
Never	371 (17%)	115 (48%)	
Biologic, n (%)	627 (28%)	88 (35%)	0.03
Anti-TNF, n (%)	577 (26%)	79 (31%)	0.07
Methotrexate, n (%)	1151 (52%)	118 (47%)	0.12
Prednisone, n (%)	897 (41%)	72 (29%)	<0.001
Clinical Composite and Component Measures			
DAS28-ESR	3.9 (1.5)	3.9 (1.4)	0.92
DAS28-CRP	3.6 (1.4)	3.4 (1.4)	0.10
CDAI	16.4 (13.3)	15.2 (13)	0.30
RAPID3	12.3 (5.9)	12.5 (6.2)	0.63
ESR, mm/hour	26.4 (23.7)	28.4 (22)	0.25
CRP, mg/dl	1.6 (2.9)	1.1 (1.6)	0.048
Tender Joint Count, 28 joints	5.0 (6.7)	4.4 (6.4)	0.26
Swollen Joint Count, 28 joints	3.9 (5.3)	3.1 (4.6)	0.02
EvGA, 0-10 scale	3.5 (2.3)	2.9 (2.2)	<0.01
PtGA, 0-10 scale	4.0 (2.5)	3.9 (2.7)	0.48
Pain, 0-10 scale	4.5 (2.8)	4.5 (3.1)	0.98
MD-HAQ, 0-3 scale	0.9 (0.6)	0.8 (0.7)	0.02

Data represented as mean (SD) or median (IQR) for skewed data.
*BMI: n men=1512, n women =162
†Disease duration years: n men=2448, n women=246

Abbreviations: N= total number of patients, BMI= Body Mass Index, Anti-CCP= anti- cyclic citrullinated protein, Anti-TNF= Anti-Tumor Necrosis Factor Inhibitor, Biologic= anti-TNF or rituximab or tocilizumab, or abatacept, DAS28=Disease Activity Score 28 joints, DAS28-CRP=Disease Activity Score 28 joints c-reactive protein, CDAI= Clinical Disease Activity Index, and RAPID3=Routine Assessment of Patient Index Data 3, ESR= erythrocyte sedimentation rate, CRP= c-reactive protein, PtGA= patient global assessment score, EvGA= physician global assessment, MD-HAQ= multi-dimensional health assessment questionnaire, Pain= Visual analogue pain scale

Table 2. Odds of being in remission or low activity for women versus men in VARA at any observation; adjusted for age, race, smoking, and disease duration. A normal age- and sex-specific ESR was defined as: ESR <30 mm/hour and <20 mm/hour for women and men over 50, respectively and ESR <20 mm/hour and <15 mm/hour for women and men younger than 50, respectively.

	N/Obs	**Men Low Activity** Obs/Total Obs (%)	**Women Low Activity** Obs/Total Obs (%)	aOR (95% CI)	p-value
Remission					
DAS28-ESR (<2.6)	2398/26148	5766/23719 (24%)	491/2429 (20%)	0.71 (0.55, 0.91)	<0.01
DAS28-CRP (<2.6)	2330/24875	7177/22579 (32%)	761/2278 (33%)	1.14 (0.91, 1.42)	0.25
CDAI (≤2.8)	2227/20261	2139/18469 (12%)	220/1792 (12%)	1.28 (0.96, 1.71)	0.09
RAPID3 (≤3)	2348/26261	1248/23853 (5%)	136/2408 (6%)	0.97 (0.67, 1.39)	0.85
Low Disease Activity					
DAS28-ESR (≤3.2)	2398/26148	9851/23719 (42%)	933/2429 (38%)	0.87 (0.71, 1.08)	0.21
DAS28-CRP (≤3.2)	2330/24875	11132/22597 (49%)	1165/2278 (51%)	1.19 (0.96, 1.48)	0.12
CDAI (≤10)	2227/20261	8656/18469 (47%)	848/1792 (47%)	1.36 (1.08, 1.73)	0.01
RAPID3 (≤6)	2348/26261	3808/23853 (16%)	398/2408 (17%)	1.04 (0.80, 1.35)	0.76
Clinical Components					
ESR (<30 mm/hour)	2442/26714	16273/24222 (67%)	1607/2492 (64%)	0.72 (0.57, 0.90)	<0.01
ESR (age- and sex-specific)	2442/26714	12001/24222 (50%)	1566/2492 (63%)	1.32 (1.05, 1.64)	0.02
CRP (≤1.0 mg/dL)	2366/25196	14489/22863 (63%)	1639/2333 (70%)	1.26 (1.01, 1.59)	0.04
Tender Joint Count (≤1)	2475/28991	13788/26266 (52%)	1405/2725 (52%)	1.07 (0.88, 1.31)	0.48
Swollen Joint Count (≤1)	2476/28999	14117/26274 (54%)	1557/2725 (57%)	1.51 (1.22, 1.88)	<0.001
EvGA (≤1; 0 to 10 scale)	2238/20363	4933/18552 (27%)	539/1811 (30%)	1.54 (1.23, 1.93)	<0.001
PtGA (≤1; 0 to 10 scale)	2457/28705	4455/26025 (17%)	538/2142 (20%)	1.22 (0.95, 1.56)	0.11
Pain (≤1; 0 to 10 scale)	2469/28867	4646/26163 (18%)	436/2704 (16%)	0.87 (0.68, 1.10)	0.24
MD-HAQ (≤0.5; 0 to 3 scale)	2437/28414	6876/25755 (27%)	885/2659 (33%)	1.12 (0.87, 1.44)	0.36

Abbreviations: OR= Odds Ratio, CI= confidence interval, DAS28=Disease Activity Score 28 joints, DAS28-CRP=Disease Activity Score 28 joints with C-Reactive Protein, CDAI= Clinical Disease Activity Index, and RAPID3=Routine Assessment of Patient Index Data 3 ESR= Erythrocyte Sedimentation Rate, CRP= C-Reactive Protein, PtGA= Patient Global Assessment, EvGA= Evaluator Global Assessment, MD-HAQ= Multi-Dimensional Health Assessment Questionnaire

Table 3. Achievement of sustained remission (two consecutive visits) or low activity for women versus men adjusted for age, race, smoking, and disease duration in VARA.

	Men Low Activity N (%)	**Women Low Activity** N (%)	**Sustained Low Activity/Remission** HR (95% CI)	p-value
Remission				
DAS28-ESR (<2.6)	340/1391 (24%)	27/147 (18%)	0.53 (0.35 – 0.80)	<0.01
DAS28-CRP (<2.6)	379/1170 (32%)	43/111 (39%)	1.15 (0.82 – 1.60)	0.42
CDAI (≤2.8)	118/1078 (11%)	16/117 (14%)	1.26 (0.72 – 2.19)	0.43
RAPID3 (≤3)	110/1759 (6%)	13/184 (7%)	1.05 (0.57 – 1.93)	0.87
Low Disease Activity				
DAS28-ESR (≤3.2)	397/915 (43%)	37/93 (40%)	0.73 (0.51 – 1.03)	0.08
DAS28-CRP (≤3.2)	426/915 (47%)	41/93 (44%)	0.94 (0.67 – 1.31)	0.70
CDAI (≤10)	275/705 (39%)	26/76 (34%)	0.77 (0.51 – 1.18)	0.23
RAPID3 (≤6)	215/1517 (14%)	21/159 (13%)	0.78 (0.49 – 1.26)	0.31
Clinical Components				
ESR (<30 mm/hour)	453/872 (52%)	31/80 (39%)	0.50 (0.34 – 0.74)	0.001
ESR (age- and sex-specific)	255/872 (29%)	31/80 (39%)	1.03 (0.67 – 1.57)	0.90
CRP (≤1.0 mg/dL)	268/578 (46%)	33/54 (61%)	1.21 (0.81 – 1.80)	0.36
Tender Joint Count (≤1)	585/1114 (53%)	55/112 (49%)	0.93 (0.70 – 1.24)	0.61
Swollen Joint Count (≤1)	603/1108 (54%)	66/109 (61%)	1.10 (0.84 – 1.43)	0.49
EvGA (≤1; 0-10 scale)	174/1047 (17%)	22/111 (20%)	1.25 (0.78 – 2.01)	0.35
PtGA (≤1; 0-10 scale)	229/1737 (13%)	35/184 (19%)	1.49 (1.02 – 2.18)	0.04
Pain (≤1; 0-10 scale)	329/1658 (20%)	32/177 (18%)	0.93 (0.63 – 1.36)	0.70
MD-HAQ (≤0.5; 0-3 scale)	224/1375 (16%)	24/133 (18%)	0.95 (0.61 – 1.48)	0.83

Abbreviations: HR= hazard ratio, CI= confidence interval, DAS28=Disease Activity Score 28 joints, DAS28-CRP=Disease Activity Score 28 joints with C-Reactive Protein, CDAI= Clinical Disease Activity Index, and RAPID3=Routine Assessment of Patient Index Data 3 ESR= Erythrocyte Sedimentation Rate, CRP= C-Reactive Protein, PtGA= Patient Global Assessment, EvGA= Evaluator Global Assessment, MD-HAQ= Multi-Dimensional Health Assessment Questionnaire

Table 4: Baseline characteristics of the combined study populations from the combined population from GO-BEFORE, and GO-FORWARD.

	Men	**Women**	**p-value**
N	58	295	
Age (years)	51.3 (14.2)	48.9 (10.9)	0.14
Caucasian, N (%)	36 (62%)	181 (61%)	0.92
BMI (kg/m^2)	26.3 (5.5)	26.2 (5.6)	0.93
GO-BEFORE, %	55%	56%	0.86
Disease Activity			
DAS28-ESR	5.70 (1.36)	6.13 (1.10)	0.009
DAS28-CRP	5.26 (1.24)	5.50 (1.02)	0.11
CDAI	32 (15.2)	35 (13.0)	0.16
Clinical Components			
ESR, mm/hr	40.2 (27.9)	43.8 (27.8)	0.37
CRP, mg/dL	2.21 (2.52)	1.82 (2.38)	0.26
Tender Joint Count, 28 joints	10 (5, 17)	12 (7, 19)	0.07
Swollen Joint Count, 28 joints	8 (5, 11)	8 (5, 12)	0.90
EvGA, 0-10 scale	5.7 (4.3, 7)	6.2 (4.9, 7.4)	0.25
PtGA, 0-10 scale	5.3 (2.9, 7.5)	6.5 (4.8, 7.9)	0.01
*continuous variables presented as mean (SD) or as median (IQR) for skewed data.			

Abbreviations: BMI= Body Mass Index, DAS28=Disease Activity Score 28 joints, DAS28-CRP=Disease Activity Score 28 joints c-reactive protein, CDAI= Clinical Disease Activity Index, ESR= erythrocyte sedimentation rate, CRP= C-Reactive Protein, PtGA= patient global assessment score, EvGA= physician global assessment

Table 5 Logistic regression evaluating the odds of women achieving remission or low disease activity at 52 weeks by different composite and component clinical and MRI measures of disease activity from GO-BEFORE, and GO-FORWARD.

	Men (N=58) Low Activity N (%)	**Women (N=294) Low Activity** N (%)	**Remission 52 Weeks (58 Men; 295 Women)** OR for Women (95% CI)	p-value
Clinical Composite Scores				
DAS28-ESR (<2.6)	23/57 (40%)	67/294 (23%)	0.39 (0.21, 0.72)	0.003
DAS28-CRP (<2.6)	24 (41%)	103 (35%)	0.71 (0.39, 1.28)	0.26
CDAI (≤2.8)	19 (33%)	61 (21%)	0.50 (0.26, 0.94)	0.03
Clinical Components				
ESR (<30 mm/sec)	42/57 (74%)	162 (55%)	0.40 (0.21, 0.77)	0.006
ESR (age, sex-specific)	31/57 (54%)	134/294 (46%)	0.71 (0.39, 1.27)	0.25
CRP (≤1.0 mg/dL)	44 (76%)	237 (80%)	1.31 (0.66, 2.60)	0.44
Tender Joint Count (≤1)	29 (50%)	111 (38%)	0.57 (0.32, 1.01)	0.056
Swollen Joint Count (≤1)	31 (53%)	159 (54%)	0.96 (0.54, 1.72)	0.90
EvGA ≤1 (0-10 scale)	25 (43%)	116 (39%)	0.81 (0.45, 1.45)	0.48
PtGA ≤1 (0-10 scale)	27 (47%)	77 (26%)	0.37 (0.20, 0.68)	0.001
MRI Measures				
Synovitis (≤3)	29 (50%)	146 (49%)	0.93 (0.52, 1.67)	0.82
Osteitis (≤3)	30 (52%)	143 (49%)	0.84 (0.45, 1.57)	0.59
*adjusted for age, white v. non-white race, study, and treatment group.				

Abbreviations: DAS28=Disease Activity Score 28 joints, DAS28-CRP=Disease Activity Score 28 joints c-reactive protein, CDAI= Clinical Disease Activity Index, ESR= erythrocyte sedimentation rate, CRP= C-Reactive Protein, PtGA= Patient Global Assessment score, EvGA= Evaluator Global Assessment

Figures

Figure 1: Percent of men and women achieving low disease activity defined by different composite and component clinical measures as well as low MRI synovitis and osteitis in the GO-BEFORE and GO-FORWARD studies.

*p<0.05