Physician Preferences and Variations in Prescription of Biologic Drugs for Rheumatoid Arthritis: A Register-Based Study of 4,010 Patients in Sweden

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Physician preferences and variations in prescription of biological drugs for rheumatoid arthritis – a register-based study of 4010 patients in Sweden

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Abstract

Objective
The prescription of biological drugs for rheumatoid arthritis (RA) patients has varied considerably across different regions. Previous studies have shown physician preferences to be an important determinant in the decision to select biological disease-modifying anti-rheumatic drugs (bDMARDs) rather than non-biologic, synthetic DMARDs (sDMARDs) alone. The aim of this study was to test the hypothesis that physician preferences are an important determinant for prescribing bDMARDs for RA patients in Sweden.

Methods
Using data from the Swedish Rheumatology Quality Register, we identified 4010 RA patients who were not prescribed bDMARDs during the period 2008-2012, but who, on at least one occasion, had an sDMARD prescription and changed treatment for the first time to either a new sDMARD or a bDMARD. Physician preference for the use of bDMARDs was calculated using data on each physician’s prescriptions during the study period. The relationship between prescription of a bDMARD and physician preference, controlling for patient characteristics, disease activity and the physician's local context was evaluated using multivariate logistic regression.

Results
When adjusting for patient characteristics, disease activity and the physician’s local context, physician preference was an important predictor for prescription of bDMARDs. Compared with patients of a physician in the lowest preference tertile, patients of physicians in the highest and middle tertiles had an odds ratio for receiving bDMARD of 2.8 (95% CI 2.13-3.68) and 1.28 (95% CI 1.05-1.57), respectively.

Conclusion
Physician preference is an important determinant for prescribing bDMARDs.

Keywords
Rheumatoid Arthritis; Biologicals; Disease-Modifying Antirheumatic Drugs (DMARDs); Access to Care, Registry
Significance and Innovations

- The prescription of biological drugs (bDMARDs) for rheumatoid arthritis (RA) patients has varied considerably across different regions.
- In order to provide a more efficient and equal treatment to patients with RA and to guide clinical policy making, there is a great need to advance our understanding of the various factors that influence prescription decisions.
- In this large quantitative study, patients prescribed bDMARDs and those prescribed sDMARDs differed in patient characteristics and disease activity.
- Controlling for patient characteristics and disease activity, physician preference significantly influenced the prescription of bDMARDs, regardless the region of activity of the physician.
Management of patients with rheumatoid arthritis (RA) has undergone major transformation during the past two decades. Treatment strategies have shifted from initially being ‘careful’ to early-instituted, potent, disease-modifying antirheumatic drugs (DMARDs) including combination therapies and introduction of modern biological DMARDs (bDMARDs) (1-3). The use of bDMARDs has increased rapidly over the last decade, with a gradual increase in earlier initiation (4). Several randomized controlled trials have shown that bDMARDs reduce disease activity and improve quality of life (5-7). Recent studies, however, indicate that the effect in routine care might not be as positive as previously reported in clinical trials (8, 9). Some studies even report outcomes in patients treated with bDMARDs as similar to those attained in patients treated with synthetic DMARDs, (sDMARDs), but with bDMARDs at a 30-40-fold increased cost (10, 11).

Sweden has among the highest prescription rates of bDMARDs per capita in Europe (12). However, prescription of these drugs to RA patients has varied considerably between the Swedish regions (county councils), despite therapy guidelines from the Swedish Society for Rheumatology (2004) and the Swedish National Board of Health and Welfare (2010) (13-16). Twice as many RA patients per capita receive bDMARDs in regions prescribing the most as compared to regions prescribing the least (17). Although the need for greater efficacy is likely to be a reason for changing RA medication, a number of other considerations probably have impact on this decision. Previous overviews of research on medical services have shown that regional variations in access to health care depend on organisational, economic and social factors, as well as on characteristics of the intervention and of the individual physicians (18, 19). Recent studies have shown that variations exist not only between different regions but also between different clinical departments in the same region, as well as between different physicians (20). Factors that influence RA-drug prescription have previously been explored in
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qualitative studies (21, 22). These studies have pointed out the importance of the individual prescriber’s own [treatment] preferences. This has also been demonstrated in rheumatology-related quantitative evaluations of prescription behaviour (23-25). In an American longitudinal register study (n=1,532), adjusted for tender and swollen joint counts and global disease activity, the physicians’ preferences for bDMARDs were an independent predictor for prescribing these agents (23).

It is unclear whether the impact of physician preference, as described regarding biological therapy in the United States, is similarly important in Sweden. Swedish healthcare is dominated by public providers and tax funding, and treatment of rheumatic diseases (with biological or non-biological DMARDs) is primarily managed by rheumatologists. The Swedish Rheumatology Quality Register (SRQ) offers a unique opportunity to extensively explore the variations in prescription of biological drugs and the factors underlying these variations. This register covers the majority of public hospital rheumatology clinics and private rheumatologists in Sweden, and contains data on approximately 50,000 RA patients, corresponding to 84% of all prevalent RA cases (2012) (26). It covers patient-related demographic data, disease activity, and data on medications and has been widely used in previous research and follow-up of rheumatic care (27, 28).

The aim of this study was to test the hypothesis that the physician’s preference is an important determinant for the prescription of biological drugs in Sweden.
Patients and methods

Study database

The SRQ was initiated in 1996 by the Swedish Society for Rheumatology. It is linked to all Swedish rheumatology outpatient clinics offering anti-rheumatic drug therapy, public as well as private. Clinically relevant data are collected from patients aged 18 years or older who fulfil the 1987 American College of Rheumatology criteria for RA, and who have agreed to be included in the register. The percentage of prevalent RA patients included in the register, estimated by linking SRQ data to the Patient and Pharmaceutical Registers by the National Board of Health and Welfare, was 84% in 2012. Among patients receiving biological anti-rheumatic therapy and patients with recently diagnosed RA, 86% and 83%, respectively, were included in the register (26).

Patients agreeing to inclusion in the register are assigned a code to allow data abstraction without revealing the patient’s identity. Information on the name of the patient's clinic, the attending physician and the date of inclusion is collected. At baseline, data on patient characteristics are registered: sex, age at visit, age at onset of RA and smoking habits, laboratory markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum rheumatoid factor (RF), and antibodies to cyclic citrullinated peptides (anti-CCP). At inclusion and follow-up visits, the following information is also registered: erosive disease, disease activity assessed by the 28-joint Disease Activity Score (DAS28) and its distinct items, i.e. tender and swollen joint counts, ESR and patient’s global assessment of health. The physician’s global assessment of disease (PGA) activity is also registered. Further, disability measured with Health Assessment Questionnaire (HAQ), pain measured with Visual Analogue Scale (VAS), and health-related quality of life (HRQL) measured with EQ-5D are registered (29). Anti-rheumatic drug therapy, decided upon by the rheumatologist, is also documented at each visit.
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**Eligible population**

Patients present in the register between January 2008 and December 2012 (n=30,127) were eligible for the study. We chose a cohort of patients who were biologic-naïve during this period, but who had at least one sDMARD and changed treatment to either a bDMARD or another sDMARDs during the period (n=4010), including patients whose change was an add-on to existing treatment. The study protocol was approved by the regional ethical review board in Linköping (2013/240-31).

**Physician prescribing preference for biological drugs**

The physician’s inclination to prescribe bDMARDs instead of sDMARDs alone during the period was used as a proxy for physician preferences for bDMARDs. The physician preferences were estimated for every physician who treated at least 50 unique patients during the period, using the “initiator proportion” and “prevalence proportion” as previously described by Curtis et al. (23). Since the two ways of calculating physician preferences resulted in similar outcomes, we present only the influence of the prevalence proportion, i.e. the number of patients receiving biological therapy among the total number of patients visiting that same physician during 2008-2012. Prior to regression-analysis, the physicians were divided into three groups depending on whether they belonged to the third of the physicians with the highest, medium or lowest number of patients treated with biological drugs.

**Statistical analysis**

We first performed a descriptive analysis of factors characterizing patients who changed from one sDMARD to another sDMARD compared to patients who changed to a bDMARD. We then evaluated factors that affected prescription decisions to change to bDMARDs, compared to changing to a new sDMARD, using multivariable logistic regression. In primary comparative
tests, we included variables describing patient characteristics (sex, age at visit, age at onset of RA, smoking and duration of RA at visit), serum autoantibodies (RF-positive and/or anti-CCP positive), disease activity (tender and swollen joint counts, DAS28, PGA and patient’s global assessment of health), bone erosions, disability (pain, HAQ, and fatigue scores), and EQ-5D. All variables were assessed at the point of treatment change. All these variables were also tested in the primary regression models. Some variables had to be excluded in the models presented in this study (Models 1-4) due to lack of data (anti CCP-positive, erosion, fatigue and EQ-5D) or since they did not add any extra information concerning the difference in prescription behavior (age at onset of RA, current smoker and patient’s global assessment of disease). All other above-mentioned variables were included in Models 1-4, although for brevity only variables with P values below 0.05 will be shown.

In Model 1, we used data on patient characteristics, disease activity and previous anti-rheumatic therapy to test mainly “objective” clinical variables. In Model 2, we added the physician’s global assessment of disease activity (PGA) and tested how PGA of 1-4 influence the prescription compared to PGA of 0, in order to consider physicians' judgments to an increased extent. We subsequently quantified physician preference for the use of biological drugs, as described above, and then assessed in Model 3, if there was a significant influence of physician preference, independent of patient characteristics and disease-related factors. Finally, in Model 4, we adjusted for whether the physician worked in a region with a high or low prescription rate for biologicals, and tested if the physician’s preference still had a significant impact with respect to the average prescription rate in each region. Additionally, we tested whether hospital type (university hospitals versus smaller hospitals) influenced prescription, as has been shown elsewhere (35). However, since no significant influence of hospital type could be shown regarding the choice between prescribing bDMARDs or sDMARDs, this was not further considered.
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Results

Descriptive analysis

There were several significant differences between patients changing to a bDMARD and patients changing to another sDMARD. As the descriptive analysis shows in Table 1, patients changing to bDMARDs were slightly younger at the prescription occasion as well as at the onset of RA. Disease duration was also longer among patients changing to a bDMARD. The proportions of patients who were anti-CCP positive and/or had erosive disease during the period, respectively, were higher among those who were prescribed bDMARDs. Also the average numbers of tender and swollen joints were higher as were the levels of DAS28, HAQ, PGA and the patient’s global assessment of health. These patients also suffered more from fatigue and had lower EQ-5D-scores.

Regression analysis

Among RA patients, who were not prescribed bDMARDs during the period 2008-2012, but who on at least one occasion, had been prescribed an sDMARD, we identified 4010 patients who changed treatment to either biological (n=2620) or another non-biological DMARD therapy (n=1861).

Using a restricted set of demographic and clinical variables, results in Model 1 in the first column of Table 2, show the factors independently associated with prescription of bDMARDs. Being female was associated with a lower likelihood of prescription of bDMARDs (p<0.05). Older age and high estimated pain were also associated with a lower likelihood of being prescribed bDMARDs (p<0.001). Disease duration, swollen joint count, high levels of DAS28 and HAQ, as well as number of previous DMARDs during the study period, were associated with a higher likelihood of receiving bDMARDs.
After adding PGA, the results in Model 2 show that most factors, apart from DAS28, remained independently significant. Moreover, most of the factors had similar odds ratios as in the first model. The model’s discrimination increased slightly (~0.02-unit change in the C statistic) after addition of PGA.

We then calculated the physician preference proportions for the 314 physicians with at least 50 unique patients during the current period. The third of the physicians with the lowest, intermediary and highest prescription of biologics, prescribed biologics to 6-40%, 40-54% and 54-100% of their patients during 2009-2013, respectively. As shown in Model 3, the prevalence proportion was a significant factor for patients being prescribed biologicals, regardless of clinical factors such as disease duration, pain, swollen joint count, HAQ, number of previous DMARDs, and PGA. The odds ratio for bDMARD prescription was highest for patients whose physician was among the third of the physicians with the highest prescription rates. The C statistic increased from 0.71 in Model 1 to 0.75 in Model 3.

As shown in Figure 1, there was a high correlation between the prescription rate of the physician and the prescription rate of the region where the physician was active. Approximately 60% of the physicians with low prescription rates were active in regions with low prescription rates, while the same percentage of physicians with high prescription rates was active in regions with high prescription rates. Therefore it is highly relevant to include data on the regional prescription rate when testing the influence of physician preference on prescription of bDMARDs.

Model 4 in Table 2, including data on the ‘regional prescription rate’ revealed that physician preference was independently significant. The C statistic further increased slightly, from 0.75 in Model 3 to 0.77 in Model 4.
Discussion

In this large observational register study of Swedish prevalent RA patients who were biologic-naïve during 2008-2012, we found that physician preference was a significant determinant of prescription of bDMARDs and was independent of patient characteristics (sex and age) and disease activity (pain, swollen joints, DAS28, HAQ). Moreover, physician preference was shown to be significant, regardless of whether the physician was active in a region with high or low levels of bDMARD prescription.

This study confirms the findings of an interview study where 26 Swedish senior rheumatologists identified physician attitude towards bDMARDs as an important factor determining if a patient would be prescribed sDMARDs or bDMARDs (22). This register study extends and complements the previous findings by reporting on physicians' actual prescribing behavior as shown in the extensive Swedish Rheumatology Quality Register.

Previous research on treatment variation in healthcare has revealed a number of explanatory factors. These include the differences in resources and/or environmental constraints (30-33) and the local context and tradition at the clinic (34). Research related to RA has shown that having a close connection to a rheumatologist is positively associated with prescription of biological drugs (36) as are some non-disease related patient traits such as lower age, and socio-demographic characteristics (37).

The present study, covering 4010 RA patients, gives additional support to the hypothesis that the individual prescriber's preferences influence treatment choice, as previously highlighted by others (23-25). Curtis et al. performed a similar register study of 1532 RA patients in North America in which either bDMARDs or an sDMARD were initiated, and demonstrated that physician preference was significant even after adjusting for tender and swollen joint counts and global disease activity (23). Curtis et al. additionally include variables concerning the
patients’ comorbidities and type of insurance, both of which influence prescription of bDMARDs. Information on comorbidities would have been highly relevant, but as such data were not available to us, this could not be evaluated. Patient insurance is not relevant in a Swedish, publicly funded, system. In contrast to Curtis et al., the present study controls for the regional prescription rates of biologicals, thereby taking into account some of the variations that might be due to different local contexts and environmental constraints. The C statistic, both in the present study and in the study by Curtis et al, was 0.77 in the final regression model, despite differences in methodology. Logistic regression models are typically considered reasonable when the C statistic is higher than 0.7 and strong when C exceeds 0.8 (43).

Previous research has suggested that the impact of physician preferences may be due to differences in the evidence used for decisions, and such differences will be particularly prevalent when there is rapid technological development within the area of interest (38). They may also derive from factors associated with attributes of the individual physicians, such as their age, specialty, training environment, clinical knowledge and tolerance of risk (34, 39). We tried to eliminate some of these factors by including only physicians who treated more than 50 patients with RA during the period 2008-2012 in order to ensure a minimum level of specialisation in RA.

The strengths of our analysis include the use of a comprehensive register, enabling analysis of a large number of RA patients. Various rheumatology registers have been established in Sweden as well as in other countries in the past decade, providing an opportunity to analyse the treatment of patients with rheumatic diseases. The advantages of such registers are that multiple questions can be addressed and that they mirror real-life situations, which enables generalisable results (40, 41). The growing number of observational drug registers has resulted in a task force appointed by EULAR (the European League against Rheumatism) with recommendations for
studies from biological registers of RA. These recommendations include the setting, the participants, the variables, the statistical methods, the descriptive data and the analysis (42).

Some of these recommendations indicate drawbacks in our study that need to be discussed. The setting in the study is Swedish, and in Sweden all RA patients are eligible for treatment with bDMARDs based on the decision of the rheumatologist in charge. Varying criteria for drug treatment in different countries might have implications for the direct applicability of our results in different settings (44). However, the general conclusion from our study, that physician preference influences prescription independent of disease activity and patient characteristics, has been supported in previous rheumatology studies as well as studies from other healthcare areas (20, 23-25). Furthermore, in real-life RA therapy, patients start and stop drug treatments, switch drugs and restart previous treatments. Despite improvement within the past decade, a number of patients are still not included in the register until they are prescribed biologics. The total number of prevalent patients in the SRQ during the period 2008-2012 was 30 127. We used the cleanest exposed cohort; i.e. biologic-naïve patients with at least one sDMARD, who started treatment during this period with either bDMARD or sDMARD (n=4010). By choosing this smaller cohort, we adjusted for the fact that a number of patients first enter the register when biologicals are prescribed, thus giving more reliable results.

Based on our preceding qualitative study on Swedish rheumatologists, we chose to include all variables of clinical interest at the start. The fact that DAS28 was no longer significant in Models 2-4 is interesting, since most recommendations on treatment of RA patients are formulated based on DAS28-levels. However, this somewhat counterintuitive result could be due to the significant influence of swollen joints, which is a factor included in DAS28. Furthermore, the slightly lower odds of prescribing bDMARDs to patients with higher pain are
unexpected, given the association of pain with a higher prescription of bDMARDs in the descriptive analysis. This inversion of association shows that, although patients that have higher levels of pain are prescribed bDMARDs to a higher degree, pain in itself does not increase the odds of being prescribed bDMARDs, when everything else is controlled for. When testing for collinearity, pain was highly correlated with HAQ, DAS-28, as well as swollen joint count. From a statistic point of view, pain could therefore have been removed from the analysis, but we chose to include it in order to test the influence of a patient-generated measure compared with measures that are generally considered more “objective”, e.g. swollen joint count and DAS-28.

Some of the variables shown in the descriptive analysis, such as data on anti-CCP and erosive disease, could not be included in our regression analysis due to lack of data. This is a limitation of the study and should be further evaluated in future research. Future research could also explore what it is at regional level that influences prescription. Finally, examining the relations between the different factors included in the study could be an interesting topic for further studies.

To conclude, between 2008 and 2012 there were substantial differences in patient characteristics and severity of the disease between RA patients who were prescribed bDMARDs and those who were prescribed sDMARDs in Sweden. Patients prescribed bDMARDs were younger, had longer disease duration, higher disease activity and more disability. However, when controlling for patient characteristics and severity of the disease in regression models, as well as region of the prescribing physician, physician preference for biologicals turned out to be an important predictor for prescription of bDMARDs.
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Competing interests

The authors have declared no conflicts of interest.

Contributorship statement

AK, MH, EH, KR, and PC participated in the design of the study. AK and MH performed the statistical analyses and all authors participated in the interpretation of data. AK wrote the first draft of the manuscript. All authors were involved in critically evaluating the manuscript. All authors read and approved the final manuscript.

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Ethical approval information

The study protocol was approved by the regional ethical review board in Linköping (2013/240-31).
References


(2014-03-17 Date last accessed)


33. de Jong JD, Westert GP, Lagoe R, Groenewegen PP. Variation in hospital length of stay: do physicians adapt their length of stay decisions to what is usual in the hospital where they work? Health Serv Res 2006;41(2): 374–94.


35. Carli C, Ehlin A G C, Klareskog L, Lindblad S, Montgomery SM. Trends in disease modifying antirheumatic drug prescription in early rheumatoid arthritis are influenced


Table 1. Descriptive analysis of factors associated with patients changing treatment from one sDMARD to either a bDMARD or another sDMARD, mean and percentages.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Change to bDMARD</th>
<th>N</th>
<th>Change to another sDMARD</th>
<th>N</th>
<th>Sign</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (% women)</td>
<td>74</td>
<td>3 510</td>
<td>75</td>
<td>2 378</td>
<td>0.393</td>
</tr>
<tr>
<td>Age at visit (years)</td>
<td>56.9</td>
<td>3 182</td>
<td>58.0</td>
<td>2 179</td>
<td>0.000</td>
</tr>
<tr>
<td>*Age at onset of RA (years)</td>
<td>47.3</td>
<td>3 476</td>
<td>51.3</td>
<td>2 349</td>
<td>0.000</td>
</tr>
<tr>
<td>*Current smoker (%)</td>
<td>16</td>
<td>2 570</td>
<td>17</td>
<td>1 538</td>
<td>0.359</td>
</tr>
<tr>
<td>Duration of RA at visit (years)</td>
<td>9.6</td>
<td>3 476</td>
<td>6.8</td>
<td>2 349</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Laboratory markers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA seropositive (%)</td>
<td>80</td>
<td>3 453</td>
<td>72</td>
<td>2 329</td>
<td>0.000</td>
</tr>
<tr>
<td>*anti CCP-positive (%)</td>
<td>82</td>
<td>677</td>
<td>72</td>
<td>582</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Disease activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Erosive disease (%)</td>
<td>52</td>
<td>617</td>
<td>34</td>
<td>460</td>
<td>0.000</td>
</tr>
<tr>
<td>Tender joints (out of 28)</td>
<td>6.4</td>
<td>3 219</td>
<td>4.3</td>
<td>2 330</td>
<td>0.000</td>
</tr>
<tr>
<td>Swollen joints (out of 28)</td>
<td>5.9</td>
<td>3 220</td>
<td>3.6</td>
<td>2 331</td>
<td>0.000</td>
</tr>
<tr>
<td>Disease activity (DAS28)</td>
<td>4.6</td>
<td>2 821</td>
<td>3.9</td>
<td>2 009</td>
<td>0.000</td>
</tr>
<tr>
<td>Physician’s global assessment of disease activity (PGA, 0-4)</td>
<td>2.0</td>
<td>3 109</td>
<td>1.6</td>
<td>2 237</td>
<td>0.000</td>
</tr>
<tr>
<td>*Patient’s global assessment of health (VAS, 0-100mm)</td>
<td>50.9</td>
<td>3 156</td>
<td>44.7</td>
<td>2 169</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Disability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain (VAS, 0-100mm)</td>
<td>50.1</td>
<td>3 131</td>
<td>44.3</td>
<td>2 151</td>
<td>0.000</td>
</tr>
<tr>
<td>HAQ Disability Index (0-3)</td>
<td>1.0</td>
<td>2 976</td>
<td>0.8</td>
<td>2 053</td>
<td>0.000</td>
</tr>
<tr>
<td>*Fatigue</td>
<td>49.7</td>
<td>625</td>
<td>46.5</td>
<td>442</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Health related quality of life (HRQL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*EQ-5D</td>
<td>0.5</td>
<td>1 228</td>
<td>0.6</td>
<td>860</td>
<td>0.000</td>
</tr>
</tbody>
</table>

*: Not included in Models 1-4 due to a lack of data (anti-CCP, erosive disease, fatigue and EQ-5D) or that they did not add any extra information about the difference in prescription (age at onset of RA, current smoker and the patient’s global assessment of disease).
Figure 1. Physicians in low, middle and high tertiles of prescription rates working in regions with high, middle and low prescription rates.
Table 2. Regression analysis of factors associated with patients changing treatment from one sDMARD to a bDMARD, instead of another sDMARD.

<table>
<thead>
<tr>
<th></th>
<th>Model 1, n=4010</th>
<th>Model 2, n=3853</th>
<th>Model 3, n=3596</th>
<th>Model 4, n=3579</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td><strong>Patient Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (female vs. male)</td>
<td>0.81 (0.69-0.94)</td>
<td>0.84 (0.72-1.00)</td>
<td>0.88 (0.74-1.05)</td>
<td>NS 0.88 (0.73-1.05) NS</td>
</tr>
<tr>
<td>Age (per 10 years)</td>
<td>0.80 (0.76-0.84)</td>
<td><strong>0.81 (0.77-0.86)</strong></td>
<td><strong>0.83 (0.78-0.87)</strong></td>
<td>*** 0.81 (0.77-0.86) ***</td>
</tr>
<tr>
<td>Duration of RA at visit (per year)</td>
<td>1.04 (1.03-1.05)</td>
<td><strong>1.04 (1.03-1.05)</strong></td>
<td><strong>1.04 (1.03-1.05)</strong></td>
<td>*** 1.04 (1.04-1.05) ***</td>
</tr>
<tr>
<td><strong>Disease Activity and Treatments</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seropositive RA (Yes vs. No)</td>
<td>1.51 (1.29-1.77)</td>
<td><strong>1.54 (1.30-1.81)</strong></td>
<td><strong>1.58 (1.33-1.88)</strong></td>
<td>*** 1.62 (1.35-1.93) ***</td>
</tr>
<tr>
<td>No of swollen joints (out of 28)</td>
<td>1.10 (1.08-1.13)</td>
<td><strong>1.07 (1.04-1.09)</strong></td>
<td><strong>1.07 (1.04-1.10)</strong></td>
<td>*** 1.08 (1.05-1.11) ***</td>
</tr>
<tr>
<td>DAS-28</td>
<td>1.17 (1.08-1.27)</td>
<td><strong>1.04 (0.95-1.14)</strong></td>
<td>NS 0.98 (0.89-1.08) NS</td>
<td>0.96 (0.87-1.06) *</td>
</tr>
<tr>
<td>Pain (per 10-mm change on a 100-mm VAS)</td>
<td>0.94 (0.91-0.97)</td>
<td><strong>0.93 (0.90-0.96)</strong></td>
<td><strong>0.95 (0.91-0.99)</strong></td>
<td>* 0.95 (0.91-0.99) NS</td>
</tr>
<tr>
<td>HAQ Disability Index (0-3)</td>
<td>1.54 (1.34-1.78)</td>
<td><strong>1.50 (1.30-1.74)</strong></td>
<td><strong>1.51 (1.28-1.76)</strong></td>
<td>*** 1.49 (1.27-1.75) ***</td>
</tr>
<tr>
<td>No of previous DMARDs (during 2008-2012)</td>
<td>1.21 (1.07-1.38)</td>
<td><strong>1.20 (1.05-1.36)</strong></td>
<td><strong>1.27 (1.10-1.46)</strong></td>
<td>*** 1.34 (1.16-1.55) ***</td>
</tr>
<tr>
<td>PGA (0)</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>PGA (0-1)</td>
<td>0.74 (0.55-1.00)</td>
<td>* 0.82 (0.59-1.13)</td>
<td>NS 0.84 (0.60-1.18)</td>
<td>NS</td>
</tr>
<tr>
<td>PGA (0-2)</td>
<td>1.51 (1.08-2.10)</td>
<td>* 1.80 (1.27-2.57)</td>
<td>** 1.93 (1.34-2.80)</td>
<td>***</td>
</tr>
<tr>
<td>PGA (0-3)</td>
<td>2.68 (1.76-4.06)</td>
<td><strong>3.37 (2.16-5.26)</strong></td>
<td><strong>3.89 (2.45-6.20)</strong></td>
<td>***</td>
</tr>
<tr>
<td>PGA (0-4)</td>
<td>5.64 (1.21-26.19)</td>
<td>* 9.17 (1.95-43.23)</td>
<td>** 11.9 (2.46-57.47)</td>
<td>**</td>
</tr>
<tr>
<td><strong>Physician preference</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician prevalence proportion (lowest tertile)</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Middle tertile</td>
<td>1.49 (1.25-1.70)</td>
<td>*** 1.28 (1.05-1.57)</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Highest tertile</td>
<td>3.62 (2.98-4.56)</td>
<td>*** 2.80 (2.13-3.68)</td>
<td>***</td>
<td></td>
</tr>
<tr>
<td><strong>Physician location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region 0…18</td>
<td></td>
<td></td>
<td></td>
<td>Not Presenteda</td>
</tr>
</tbody>
</table>

Model 1 includes demographic and clinical variables, Model 2 includes Model 1 + Physician’s global assessment of disease activity, Model 3 includes Model 2 + Physician preferences, Model 4 includes Model 3 + Regional prescription rates. Only parameter estimates for factors associated with the outcome, p < 0.05 in at least one model, are shown for brevity, and to reduce collinearity; however, the C statistic (the area under the ROC curve) reflects discrimination for the model with all a priori specified variables. RA= rheumatoid arthritis; OR= odds ratio; 95% CI= confidence interval; VAS= visual analogue scale; HAQ= health assessment questionnaire; DMARDs= disease modifying antirheumatic drugs; PGA= Physician’s global assessment of disease activity * p<0.05, ** p<0.01, *** p<0.001, NS= not significant at p<0.05. a= compared to the region with the highest prescription of bDMARDS, the OR for the other regions was 0.16-0.66, p=0.000-0.73.
Physician preferences and variations in prescription of biological drugs