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Drug Prescribing Trends in Adults with Rheumatoid Arthritis: A Population-Based Comparative Study from 2005–2014

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Abstract

Objective—To examine drug prescribing trends for patients with rheumatoid arthritis (RA) over recent years and compare them to matched non-RA subjects.

Methods—Retrospective prescription data were examined from 2005–2014 in a population-based incidence cohort of patients with RA and comparable non-RA subjects. Drugs for or related to the treatment of RA were excluded. Comparisons between cohorts of percentages of patients with at least 1 prescription in a specific drug category/class were performed using Poisson regression models adjusted for age and sex.

Results—The study included 497 RA (71% female) and 527 non-RA subjects (70% female). The overall observed percentage of subjects who were prescribed at least 1 drug over the ten-year period was somewhat higher among the RA compared to non-RA subjects (relative risk [RR]: 1.04; 95% confidence interval [CI]: 0.99, 1.08). Over the study period, both groups demonstrated significant increases in the percentages of patients with at least 1 prescription (age and sex adjusted 7% increase over 10 years in RA, $p < 0.001$; 11% increase in non-RA, $p < 0.001$). Drugs that were more common among RA than non-RA included gastrointestinal drugs, antimicrobials, calcium metabolism modifiers, thyroid hormone replacement therapy, tricyclic antidepressants, antiasthma/inhaled corticosteroids, proton pump inhibitors, contraceptives, anti-hypertensives and some others. Prescription drugs that were less common in RA than non-RA were statins and other antilipemic drugs.

Conclusion—Excluding drug prescriptions specifically for treatment of RA, there was a marked overall increase in prescriptions for drugs for both RA and non-RA cohorts over the study period.

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Keywords

Rheumatoid arthritis; drug use; prescription patterns; statins

Over recent years the use of prescription drugs has been steadily on the rise around the world and especially so in first-world countries including most of Europe, the United Kingdom, Canada, and the United States (US) [1] [2] [3] [4]. In line with this increase and according to the World Health Organization (WHO), the pharmaceutical market will grow by at least \$100 billion USD, or from 300 to 400 billion a year market, in just the next three years; 85% of the global market will be in Europe, Japan, North and South America [5].

Nearly 60% of US adults are reported to take at least one prescription drug in 2012, and 15% of adults take five or more prescription drugs, up from 51% and 8% respectively just ten years prior [6]. Another recent study published in 2013 has placed an even higher percentage of all US adults (18 years of age) taking at least one prescription closer to 70% [7]. Older Americans are often the group most affected by this increase. A recent report from the U.S. Department of Health and Human Services (HHS) stated that 9 out of 10 adults 60 years of age or older self-reported taking at least one prescription drug in the last month [1]. HHS has also recently reported that prescription drug spending accounts for 16.7% of all US health care spending in 2015 compared to 15.3% in 2013, a stark contrast to 7% just 20 years earlier in 1995 [8].

Several subsets of the population and classes of drugs have been of interest in studies examining this relative recent and large increase in prescription drug use. Prescription trends can, for instance, indirectly reflect the burden of disease in a particular population [9]. One such population, for whom only limited data are available, are persons with rheumatoid arthritis (RA). Patients with RA often take several drugs for management of their disease, as well as comorbid conditions which are more frequent in these patients. For example, patients with RA are known to suffer higher rates of cardiovascular disease, infections, depression, and fibromyalgia than the general population [10–13]. Furthermore, prescription drug patterns can be used in evaluating adherence to established therapy guidelines in RA and identify areas in need for improvement [14]. The population health burden of RA is particularly important because the Centers for Disease Control and Prevention (CDC) estimated that RA affected 1.5 million Americans in 2007 and this number is projected to continue to grow over time [15].

The aim of this study was to identify trends in nonrheumatoid prescription drugs among patients with RA compared to similar subjects without RA over recent years and to describe the differences in prescription patterns between the two groups.

Methods

Study Population

This retrospective cohort study was approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. Study subjects were identified using resources from the Rochester Epidemiology Project (REP), a unique record-linkage system that provides access

to all inpatient and outpatient encounters among the residents of Olmsted County, Minnesota, including prescription information [16,17]. All Olmsted County, Minnesota residents aged 18 years or older who first fulfilled 1987 American College of Rheumatology criteria for RA in 1980–2004 were previously identified [18]. A comparison cohort of patients without RA with similar age, sex, and calendar year was randomly selected from the same population. The index date was defined to be January 1st 2005 and included all patients from the RA and non-RA cohorts who were alive and followed for at least 3 months after that date. All subjects in both cohorts were followed longitudinally until death, migration, or December 31, 2014.

Data collection

All outpatient prescription drug data with both generic and trade names were collected for 2005 to 2014. Prescription drugs for and related to the treatment of RA, as well as drugs commonly available without a prescription were excluded from the analysis. The following drug classes were excluded: nonbiologic and biologic disease modifying antirheumatic drugs, nonsteroidal antiinflammatory drugs, cyclooxygenase 2 inhibitors, glucocorticoids, opioid analgesics, antineoplastics, antimalarials, salicylates, vitamins, folic acid and antigout drugs. Drug categories examined in the study are described in table 1. Drug classes were grouped based on national data for comparison purposes and to allow sufficient frequency for analysis when necessary [6].

Subjects with <3 months of follow-up in a particular calendar year were excluded from the analysis of that calendar year. Diagnoses of comorbidities prior to index were obtained electronically for both cohorts and classified using the Deyo adaptation of the Charlson comorbidity index [19]. These included myocardial infarction, peripheral vascular disease, cerebrovascular disease, peptic ulcer disease, diabetes mellitus and cancer. Smoking status and educational achievement were obtained from self-answered questionnaires routinely administered at clinic visits.

Statistical analysis

Descriptive statistics (means, percentages, etc.) were used to summarize the characteristics of each cohort. Characteristics were compared between cohorts using Chi-square and rank sum tests. Age adjustment was necessary in order to assess trends over time because this study cohort aged over the 10 year period of the study. Yearly estimates of the percentage of subjects with prescription drugs by category/class were adjusted to the age and sex distribution of the entire study cohort using Poisson regression models with smoothing splines for calendar year to allow for non-linear effects. Poisson regression models adjusted for age and sex were also used to estimate the relative risk of drug use among those with RA compared to those without RA. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 1,024 subjects, 497 patients with RA (71% female) and 527 non-RA comparator subjects (70% female), were included in the study. Median age on 1/1/2005 for RA and non-RA subjects was 61 years (range 25–95) and 63 years (range 26–95), respectively. Among the patients with RA, the median duration of RA at index date was 7.5 years (range 0 to 24.8). Median time from 1/1/2005 to last follow-up for both RA and non-RA subjects was 9.9 years. Comorbidities prior to index were similar among both groups with notable exceptions of peptic ulcer disease (13% non-RA vs 19% RA) and peripheral vascular disease (12% non-RA vs 19% RA). Former and/or current smoking was more common among RA patients at 55% compared to non-RA at 46%. Both cohorts were predominantly Caucasian (96% non-RA, 94% RA) (table 2).

The overall observed percentage of subjects who were prescribed at least 1 non-RA related drug over the ten-year period, was higher among patients with RA compared to non-RA subjects, but this difference did not reach statistical significance (age and sex adjusted relative risk [RR]: 1.04; 95% confidence interval [CI]: 0.99, 1.08). Overall women with RA were more likely to have at least one prescription than women without RA (age and sex adjusted RR: 1.05; 95% CI: 1.00, 1.11) with no differences observed between RA and non-RA men (age and sex adjusted RR: 0.99; 95% CI: 0.91, 1.08; figure 1). There were somewhat more young RA patients than comparator subjects aged 18–49 years with at least 1 prescription (age and sex adjusted RR: 1.12; 95% CI: 0.99, 1.26) but no differences in the percentages of patients with at least 1 prescription were seen in the older age groups.

Over the observed time period, prescriptions for the gastrointestinal, antimicrobial, endocrine, respiratory, and anti-depressant drug categories among patients with RA were significantly higher than for comparator subjects (age and sex adjusted RR: 1.25; 95% CI: 1.16, 1.34; RR: 1.24; 95% CI: 1.16, 1.32; RR: 1.23; 95% CI: 1.14, 1.31; RR: 1.21; 95% CI: 1.09, 1.33; RR: 1.12; 95% CI: 1.03, 1.22, respectively) (figure 2). There were no observed differences in the overall category rates for cardiovascular, CNS, or ophthalmic drugs (table 3).

During the study period, there were several specific drug classes for which the percentage of patients with at least 1 prescription differed between patients with RA and non-RA comparators. Fewer RA patients were prescribed statins (age and sex adjusted RR: 0.83; 95% CI: 0.76, 0.90) and non-statin antilipemic drugs (age and sex adjusted RR: 0.56; 95% CI: 0.44, 0.70), as well as insulin/oral hypoglycemics (age and sex adjusted RR: 0.84; 95% CI: 0.73, 0.97).

In contrast, more patients with RA compared to non-RA subjects received prescriptions for beta-lactams (age and sex adjusted RR: 1.28; 95% CI: 1.17, 1.41), other antimicrobials (age and sex adjusted RR: 1.49; 95% CI: 1.33, 1.66), calcium metabolism modifiers (age and sex adjusted RR: 1.78; 95% CI: 1.57, 2.02), thyroid hormone replacement therapy (age and sex adjusted RR: 1.21; 95% CI: 1.09, 1.34), antiasthma/inhaled corticosteroids (age and sex adjusted RR: 1.21; 95% CI: 1.08, 1.37) and proton pump inhibitors (age and sex adjusted RR: 1.45; 95% CI: 1.32, 1.59) (figure 3). Additionally, RA patients received more tricyclic

antidepressants (age and sex adjusted RR: 1.49; 95% CI: 1.25, 1.77), antianginals/ anticoagulants (age and sex adjusted RR: 1.23; 95% CI: 1.09, 1.40), non-proton pump inhibitor antiulcer drugs (age and sex adjusted RR: 1.58; 95% CI: 1.26, 1.98), oral contraceptives (age and sex adjusted RR: 1.69; 95% CI: 1.37, 2.08) macrolide antibiotics (age and sex adjusted RR: 1.48; 95% CI: 1.30, 1.68), fluoroquinolones (age and sex adjusted RR: 1.29; 95% CI: 1.16, 1.45), sulfonamides (age and sex adjusted RR: 1.22; 95% CI: 1.02, 1.45), estrogen/progesterone formulations (age and sex adjusted RR: 1.54; 95% CI: 1.20, 1.99) and antihypertensives (age and sex adjusted RR: 1.11; 95% CI: 1.04, 1.18).

In 2014 the five drug classes with the highest rate of subjects receiving prescriptions (after adjusting for age and sex) were antihypertensives (55% RA vs 49% non-RA), statins (29% RA vs 35% non-RA), proton pump inhibitors (28% RA vs 18% non-RA), beta-lactams (26% RA vs 19% non-RA) and thyroid hormone replacement (23% RA vs 19% non-RA).

Examining time trends over the 10 year study period, both the patients with RA and the non-RA comparators demonstrated significant increases in the percentages of patients with at least 1 prescription (age and sex adjusted 7% increase over 10 years in RA $p<0.001$; 11% increase in non-RA, $p<0.001$). According to drug class, most drug classes showed significant increases over time among both groups (Table 3). The overall increases among the RA patients were driven by the older ages (age ≥ 65 years), as the changes over time among the young (age 18–49 years) and the middle aged (age 50–64 years) were not significant (age and sex adjusted 1% decrease in young, $p=0.86$; 6% increase in middle aged, $p=0.22$; 10% increase in older ages, $p<0.001$). In contrast, there were significant increases among the non-RA comparators in all age groups (age and sex adjusted 26% increase in young, $p=0.005$; 8% increase in middle aged, $p=0.007$; 11% increase in older ages, $p<0.001$). Of note, the seemingly sizable differences in trends between the young RA (1% decrease) and the young non-RA (26% increase) did not reach statistical significance (interaction $p=0.25$).

Overall, the percentages of women with at least 1 prescription increased over time in both groups (age adjusted 7% increase in RA, $p=0.006$; 13% increase in non-RA, $p<0.001$). The increases over time in men with at least 1 prescription did not reach statistical significance in either group (6% increase in RA, $p=0.079$; 8% in non-RA, $p=0.058$).

Discussion

The results of this study demonstrate a significant increase of overall prescription drug use over time, both for patients with RA and for non-RA comparators. This increase is due to an increased number of subjects with at least one prescription in most, although not all, drug classes. More women with RA had a prescription for at least one drug when compared to age and sex matched non-RA women after excluding anti-rheumatic drugs.

The observed overall increase in prescription drug use for both cohorts is comparable to previous study from the National Health and Nutrition Examination Survey (NHANES) cycle data which reported that approximately 90% of U.S. adults, 65 years of age or older, having at least one prescription [6]. The most commonly prescribed drugs in the current

study were antihypertensives, in slightly over half of RA patients and comparators, which are percentages approximate with the American Heart Association's prevalence estimates for U.S. adults with hypertension in 2012 of 54% for those 55–64 years of age [20]. In the current study, more patients with RA, however, had a prescription for at least one drug than comparator subjects despite removal of RA related therapy; although this small difference did not reach statistical significance, it did persist over the study period. A larger difference between RA and non-RA was noted in use of opioid analgesics, which were excluded from this study. There has been a significant difference in opioid prescriptions over comparators in this same population over the same time period; 40% of patients with RA received a prescription versus 12% of non-RA comparator subjects in 2014 [21]. Antidepressants as a drug class demonstrated one of the largest overall increases over the ten year period, likely a result of the increasing recognition and treatment of depression in the general population.

Despite this overall increase in prescription drugs over time, fewer patients with RA are prescribed statins and non-statin antilipemic agents than their non-RA counterparts. Although there was an overall increase in cardiovascular category prescription drugs over time in both groups, and while this increase was primarily driven by statin and anti-hypertensive prescriptions, fewer patients with RA received prescriptions for cardiovascular drugs than comparators over the observed period. This is concerning as patients with RA are at increased risk for cardiovascular events and are often at sufficiently high risk to require statin therapy [13] [22]. A previous study from this same population found that patients with RA were not adequately initiated on lipid lowering therapy when they met clinical guidelines set by the National Cholesterol Education Program (NCEP) and their lipids were tested less frequently than individuals from the general population [23].

In addition, as previously reported, patients with RA in this cohort had a significantly higher incidence of peripheral vascular disease than comparators, which is itself associated with a higher incidence of cardiovascular events, and yet were prescribed fewer statins [24] [25]. Related to the present findings, researchers from the Dutch Trial Registry recently found that RA patients were undertreated for both hyperlipidemia and hypertension due to no treatment or insufficient therapy to meet recommended target goals [26]. In contrast, more patients with RA are prescribed inhaled corticosteroids and antiasthma drugs than their non-RA counterparts, which may indirectly suggest a higher prevalence of obstructive lung disease as both lungs and pleura are common sites for extraarticular involvement in these patients [27].

Moreover, patients with RA are more likely to be prescribed antimicrobials, especially beta-lactams, which is likely in part a reflection of higher rates of infection as a result of both anti-rheumatic therapies and the disease related alteration of the immune system in conjunction with a provider's willingness to prescribe based on the knowledge of altered immunity [28]. Lastly, the significantly higher percentage of patients with RA who were prescribed proton pump inhibitors (28% vs 18% in non-RA subjects for 2014) are likely in part a result of either prevention and/or treatment of anti-rheumatic therapy related side effects; i.e., non-steroidal antiinflammatory induced peptic ulcer disease [29]. As proton pump inhibitors have increasingly been associated with kidney disease (including chronic

kidney disease), community-acquired pneumonia, and *Clostridium difficile* infection, caution in their use may be warranted [30].

This is the first study of prescription drug trends in a well-described, modern RA cohort over the most recent decade in which prescription data was analyzed from a robust data collection system. Moreover, the population of Olmsted County is stable, with few migrations, so it is quite likely that the prescription data is accurate and complete. Limitations include the lack of specific indications for which the drugs were prescribed, as well as lack of data on compliance. Prescriptions given outside Olmsted County, MN were not included, although it is unlikely that this differed between patients with RA and comparators. Furthermore, the residents of Olmsted receive the majority of care within the county [31]. Cohorts included primarily Caucasians, so generalizability to other populations may be limited and differences between ethnicities could not be evaluated. The purpose of this study was to describe the patterns of prescription drugs and not of healthcare burden or cost, and while it is of public health importance, cost could not be directly ascertained.

Conclusion

Excluding drug prescriptions specifically for, or directly related to the treatment of RA, there was a marked overall increase in prescriptions drugs for both RA and non-RA cohorts over the study period. Overall, prescriptions for cardiovascular, ophthalmic, and CNS drug categories were similar among RA and non-RA subjects, but some prescribing patterns differed between the cohorts. Although patients with RA are at higher risk for cardiovascular events, they were consistently prescribed less statins and non-statin antilipemic than non-RA comparators. Patients with RA are consistently prescribed more proton pump inhibitors which may be associated with significant adverse effects over the long term.

Prescription patterns are helpful in understanding the burden of disease and gaps in knowledge about the medical needs of patients with RA. Further work in this field will shed more light on this important aspect of disease management and proper consolidation of patient's pharmacological therapies.

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References

1. Gu Q, Dillon CF, Burt VL. Prescription drug use continues to increase: U.S. prescription drug data for 2007–2008. *NCHS Data Brief*. 2010; (42):1–8.
2. Jorgensen T, Johansson S, Kennerfalk A, Wallander MA, Svardsudd K. Prescription drug use, diagnoses, and healthcare utilization among the elderly. *Ann Pharmacother*. 2001; 35(9):1004–1009. [PubMed: 11573845]
3. Zhang F, Mamtani R, Scott FI, Goldberg DS, Haynes K, Lewis JD. Increasing use of prescription drugs in the United Kingdom. *Pharmacoepidemiol Drug Saf*. 2015; doi: 10.1002/pds.3947

4. Smolina K, Morgan S. The drivers of overspending on prescription drugs in Quebec. *Healthc Policy*. 2014; 10(2):19–26. [PubMed: 25617512]
5. Organization WH. Trade, foreign policy, diplomacy and health: Pharmaceutical Industry. 2016.
6. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL. Trends in Prescription Drug Use Among Adults in the United States From 1999–2012. *Jama*. 2015; 314(17):1818–1831. DOI: 10.1001/jama.2015.13766 [PubMed: 26529160]
7. Zhong W, Maradit-Kremers H, St Sauver JL, Yawn BP, Ebbert JO, Roger VL, Jacobson DJ, McGree ME, Brue SM, Rocca WA. Age and sex patterns of drug prescribing in a defined American population. *Mayo Clin Proc*. 2013; 88(7):697–707. DOI: 10.1016/j.mayocp.2013.04.021 [PubMed: 23790544]
8. Services USDoHH. Observations on Trends in Prescription Drug Spending 2016. 2016.
9. Cossman RE, Cossman JS, James WL, Blanchard T, Thomas RK, Pol LG, Cosby AG, Mirvis DM. Evaluating heart disease prescriptions-filled as a proxy for heart disease prevalence rates. *J Health Hum Serv Adm*. 2008; 30(4):503–528. [PubMed: 18236701]
10. Lee YC. Effect and treatment of chronic pain in inflammatory arthritis. *Curr Rheumatol Rep*. 2013; 15(1):300.doi: 10.1007/s11926-012-0300-4 [PubMed: 23292816]
11. Teague H, Mehta NN. The Link Between Inflammatory Disorders and Coronary Heart Disease: a Look at Recent Studies and Novel Drugs in Development. *Curr Atheroscler Rep*. 2016; 18(1): 3.doi: 10.1007/s11883-015-0557-y [PubMed: 26739273]
12. Lin MC, Guo HR, Lu MC, Livneh H, Lai NS, Tsai TY. Increased risk of depression in patients with rheumatoid arthritis: a seven-year population-based cohort study. *Clinics (Sao Paulo)*. 2015; 70(2):91–96. DOI: 10.6061/clinics/2015(02)04 [PubMed: 25789516]
13. Crowson CS, Matteson EL, Roger VL, Thernau TM, Gabriel SE. Usefulness of risk scores to estimate the risk of cardiovascular disease in patients with rheumatoid arthritis. *Am J Cardiol*. 2012; 110(3):420–424. DOI: 10.1016/j.amjcard.2012.03.044 [PubMed: 22521305]
14. Katada H, Yukawa N, Urushihara H, Tanaka S, Mimori T, Kawakami K. Prescription patterns and trends in anti-rheumatic drug use based on a large-scale claims database in Japan. *Clin Rheumatol*. 2015; 34(5):949–956. DOI: 10.1007/s10067-013-2482-1 [PubMed: 24420724]
15. CDC. Arthritis-Related Statistics. 2015. http://www.cdc.gov/arthritis/data_statistics/arthritis_related_stats.htm
16. Melton LJ 3rd. History of the Rochester Epidemiology Project. *Mayo Clin Proc*. 1996; 71(3):266–274. DOI: 10.1016/S0025-6196(11)63966-9 [PubMed: 8594285]
17. St Sauver JL, Grossardt BR, Yawn BP, Melton LJ 3rd, Pankratz JJ, Brue SM, Rocca WA. Data resource profile: the Rochester Epidemiology Project (REP) medical records-linkage system. *Int J Epidemiol*. 2012; 41(6):1614–1624. DOI: 10.1093/ije/dys195 [PubMed: 23159830]
18. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum*. 1988; 31(3):315–324. [PubMed: 3358796]
19. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992; 45(6):613–619. [PubMed: 1607900]
20. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. *Circulation*. 2015; 131(4):e29–322. DOI: 10.1161/CIR.000000000000152 [PubMed: 25520374]
21. Zamora-Legoff JA, Achenbach SJ, Crowson CS, Krause ML, Davis JM 3rd, Matteson EL. Opioid use in patients with rheumatoid arthritis 2005–2014: a population-based comparative study. *Clin Rheumatol*. 2016; doi: 10.1007/s10067-016-3239-4
22. Toms TE, Panoulas VF, Douglas KM, Griffiths H, Sattar N, Smith JP, Symmons DP, Nightingale P, Metsios GS, Kitas GD. Statin use in rheumatoid arthritis in relation to actual cardiovascular risk:

- evidence for substantial undertreatment of lipid-associated cardiovascular risk? *Ann Rheum Dis*. 2010; 69(4):683–688. DOI: 10.1136/ard.2009.115717 [PubMed: 19854705]
23. Akkara Veetil BM, Myasoedova E, Matteson EL, Gabriel SE, Crowson CS. Use of lipid-lowering agents in rheumatoid arthritis: a population-based cohort study. *J Rheumatol*. 2013; 40(7):1082–1088. DOI: 10.3899/jrheum.121302 [PubMed: 23637326]
24. Hussein AA, Uno K, Wolski K, Kapadia S, Schoenhagen P, Tuzcu EM, Nissen SE, Nicholls SJ. Peripheral arterial disease and progression of coronary atherosclerosis. *J Am Coll Cardiol*. 2011; 57(10):1220–1225. DOI: 10.1016/j.jacc.2010.10.034 [PubMed: 21371639]
25. Thanassoulis G, Williams K, Kimler Altobelli K, Pencina MJ, Cannon CP, Sniderman AD. Individualized Statin Benefit for Determining Statin Eligibility in the Primary Prevention of Cardiovascular Disease. *Circulation*. 2016; doi: 10.1161/CIRCULATIONAHA.115.018383
26. van Breukelen-van der Stoep DF, van Zeben D, Klop B, van de Geijn GM, Janssen HJ, van der Meulen N, De Vries MA, Hazes M, Birnie E, Castro Cabezas M. Marked underdiagnosis and undertreatment of hypertension and hypercholesterolaemia in rheumatoid arthritis. *Rheumatology (Oxford)*. 2016; doi: 10.1093/rheumatology/kew039
27. Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, Vassallo R, Gabriel SE, Matteson EL, Bongartz T. Incidence and mortality of obstructive lung disease in rheumatoid arthritis: a population-based study. *Arthritis Care Res (Hoboken)*. 2013; 65(8):1243–1250. DOI: 10.1002/acr.21986 [PubMed: 23436637]
28. Listing J, Gerhold K, Zink A. The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. *Rheumatology (Oxford)*. 2013; 52(1):53–61. DOI: 10.1093/rheumatology/kes305 [PubMed: 23192911]
29. Masso Gonzalez EL, Patrignani P, Tacconelli S, Garcia Rodriguez LA. Variability among nonsteroidal antiinflammatory drugs in risk of upper gastrointestinal bleeding. *Arthritis Rheum*. 2010; 62(6):1592–1601. DOI: 10.1002/art.27412 [PubMed: 20178131]
30. Lazarus B, Chen Y, Wilson FP, Sang Y, Chang AR, Coresh J, Grams ME. Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease. *JAMA Intern Med*. 2016; 176(2):238–246. DOI: 10.1001/jamainternmed.2015.7193 [PubMed: 26752337]
31. St Sauver JL, Grossardt BR, Yawn BP, Melton LJ 3rd, Rocca WA. Use of a medical records linkage system to enumerate a dynamic population over time: the Rochester epidemiology project. *Am J Epidemiol*. 2011; 173(9):1059–1068. DOI: 10.1093/aje/kwq482 [PubMed: 21430193]

Figure 1. Prescription trends by age and sex for calendar years 2005–2014 in patients with rheumatoid arthritis and non-RA comparator subjects. RA shown as solid line and non-RA as dashed line.

Figure 2. Prescription trends by drug category for calendar years 2005–2014 in patients with rheumatoid arthritis and non-RA comparator subjects. RA shown as solid line vs non-RA as dashed lines (see table 1 for category makeup).

Figure 3. Prescription trends by selected drug class for calendar years 2005–2014 in patients with rheumatoid arthritis and non-RA comparator subjects. RA shown as solid line vs non-RA as dashed lines (see table 1 for class makeup).

Table 1

Included Drug Categories

Main Category	Class Grouping
Cardiovascular	Anticoagulants/Antianginals Antihypertensives Statins Other antilipemic (non-statins) Other Cardiovascular (e.g., Antiarrhythmics, Digitalis)
Gastrointestinal	Anti-acids (non-PPI) Proton Pump Inhibitors (PPIs) Laxatives Other Gastrointestinal (e.g., Anti-emetics)
Respiratory	Bronchodilators and Antiasthma Inhaled Antiinflammatories Other Respiratory (e.g., Antihistamine/Decongestant (all), Antitussives/Expectorant (all))
Endocrine	Thyroid Hormone Insulin/Oral Hypoglycemics Systemic Contraceptives Estrogen/Progesterone Calcium Metabolism Modifier Other Endocrine (e.g., Androgens)
Antimicrobials	Beta Lactams Fluoroquinolones Macrolides Sulfonamides Other Antimicrobials (e.g. Aminoglycosides, Antituberculin, Antifungals (Oral), Antivirals (Oral))
Antidepressants	Tricyclic/TCAs SSRIs/SNRI Other (MAOIs, bupropion, and trazodone)
Central Nervous System (CNS)	Pregabalin / Gabapentin Other CNS (e.g., Anticonvulsant, Antipsychotics, Antimigraine, Amphetamines, Benzodiazepine (oral), Sedatives, Stimulants (amphetamines, amphetamine-like))
Ophthalmic	Antiglaucoma Antiinflammatory (topical) Antibacterial Other Ophthalmic (e.g., other topical antimicrobials t, Eye Washes/Lubricants)

Abbreviations: PPI=Proton pump inhibitor

Table 2

Baseline (1/1/2005) Characteristics of patients with rheumatoid arthritis (RA) and non-RA comparator subjects

Characteristic	Non-RA N=527	RA N=497	P-value
Sex			0.53
Female	367 (69.6%)	355 (71.4%)	
Male	160 (30.4%)	142 (28.6%)	
Age at Baseline			0.10
Mean (SD)	62.5 (14.6)	61.1 (14.4)	
Median	63.1	61.4	
RA duration * at baseline, years			0.28
Mean (SD)	9.3 (6.7)	8.9 (6.6)	
Race			0.27
Unknown	3	2	
American Indian	1 (0.2%)	3 (0.6%)	
Asian	11 (2.1%)	14 (2.8%)	
African American	7 (1.3%)	3 (0.6%)	
Native Hawaiian	0 (0.0%)	2 (0.4%)	
White	502 (95.8%)	467 (94.3%)	
More than one race	3 (0.6%)	6 (1.2%)	
Education Level			<0.001
Missing	5	16	
<High school	43 (8.2%)	36 (7.5%)	
High school	155 (29.7%)	172 (35.8%)	
Technical school/college	241 (46.2%)	240 (49.9%)	
Graduate school	83 (15.9%)	33 (6.9%)	
Length of follow-up from baseline, years			
Mean (SD)	8.8 (2.2)	8.6 (2.6)	
Comorbidities prior to incidence *			
Myocardial infarction	46 (8.7%)	44 (8.9%)	0.94
Congestive heart failure	52 (9.9%)	52 (10.5%)	0.75
Peripheral vascular disease	65 (12.3%)	92 (18.5%)	0.006
Ulcer disease	67 (12.7%)	94 (18.9%)	0.006
Cerebrovascular disease	77 (14.6%)	67 (13.5%)	0.60
Diabetes mellitus	75 (14.2%)	69 (13.9%)	0.87
Cancer	166 (31.5%)	148 (29.8%)	0.55
Smoking status at RA incidence			0.018

Characteristic	Non-RA N=527	RA N=497	P-value
Never	285 (54.1%)	226 (45.5%)	
Former	156 (29.6%)	167 (33.6%)	
Current	86 (16.3%)	104 (20.9%)	

* For non-RA, time from index date to baseline

Table 3

Overall age and sex-adjusted percentage of subjects with at least one prescription by calendar year 2005-2014 in patients with rheumatoid arthritis and non-RA comparator subjects (displaying even years)

	2006 (n) RA=484 Non-RA=517	2008 (n) RA=455 Non-RA=498	2010 (n) RA=426 Non-RA=474	2012 (n) RA=398 Non-RA=441	2014 (n) RA=336 Non-RA=370	Change in % over 10 years	Age and sex adjusted p- value for time trend	Relative risk for RA vs non- RA (95% Confidence Interval)
Any prescription, RA Non-RA	86% 81%	85% 81%	88% 85%	88% 88%	94% 93%	7% 11%	<0.001 <0.001	1.04 (0.99-1.08)
Cardiovascular, RA Non-RA	52% 48%	51% 51%	57% 57%	59% 58%	61% 61%	9% 13%	<0.001 <0.001	1.03 (0.97-1.09)
Gastrointestinal, RA Non-RA	33% 27%	37% 29%	39% 32%	40% 32%	45% 33%	13% 6%	<0.001 0.005	1.25 (1.16-1.34)
Respiratory, RA Non-RA	16% 14%	18% 15%	20% 17%	22% 19%	27% 20%	11% 6%	<0.001 <0.001	1.21 (1.09-1.33)
Endocrine, RA Non-RA	39% 27%	38% 30%	40% 35%	40% 35%	40% 37%	2% 9%	0.32 <0.001	1.23 (1.14-1.31)
Antimicrobials, RA Non-RA	46% 38%	46% 38%	47% 38%	48% 37%	50% 41%	4% 5%	0.15 0.27	1.24 (1.16-1.32)
Antidepressants, RA Non-RA	21% 18%	22% 20%	25% 23%	28% 26%	34% 27%	13% 10%	<0.001 <0.001	1.12 (1.03-1.22)
CNS,								0.95 (0.87-1.03)

	2006 (n) RA=484 Non-RA=517	2008 (n) RA=455 Non-RA=498	2010 (n) RA=426 Non-RA=474	2012 (n) RA=398 Non-RA=441	2014 (n) RA=336 Non-RA=370	Change in % over 10 years	Age and sex adjusted p- value for time trend	Relative risk for RA vs non- RA (95% Confidence Interval)
RA	20%	20%	22%	26%	28%	9%	<0.001	
Non-RA	21%	23%	24%	26%	29%	9%	<0.001	
Ophthalmics, RA	10%	10%	14%	14%	15%	4%	<0.001	1.10 (0.97-1.24)
Non-RA	11%	10%	12%	12%	13%	1%	0.21	

Abbreviations: Rheumatoid Arthritis (RA), Central Nervous System (CNS)