

Comparative Risk of Nonvertebral Fractures Among Patients With Rheumatoid Arthritis Treated With Biologic or Targeted Synthetic Disease-Modifying Antirheumatic Drugs

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Objective. The objective of this study was to compare the incidence rate of nonvertebral osteoporotic fractures (NVFs) in patients with rheumatoid arthritis (RA) initiating one of the nine biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs).

Methods. We analyzed claims data from Optum (2008 to March 2019), Medicare, and MarketScan (2008–2017) to identify adults with RA who newly initiated b/tsDMARDs. Adalimumab was the most frequently used and was thus selected as a reference. The primary outcome was a composite of incident NVFs, including hip, humerus, pelvis, and wrist fractures, based on validated algorithms. We adjusted for greater than 70 potential confounders in each database through propensity score–based inverse probability treatment weighting. Follow-up time started the day after cohort entry until the first occurrence of one of the following: outcome, treatment discontinuation, switching, nursing home admission, death, disenrollment, or end of study period. For each drug comparison, weighted Cox proportional hazards models estimated the hazard ratios (HRs) and 95% confidence intervals (CIs). Secondary analyses were conducted in patients switching from a tumor necrosis factor inhibitor to a different b/tsDMARD.

Results. A total of 134,693 b/tsDMARD initiators were identified across three databases. The adjusted HRs showed similar risk of composite NVFs in all b/tsDMARD exposures compared with adalimumab: abatacept, HR 1.03 (95% CI 0.82–1.30); certolizumab, HR 1.08 (95% CI 0.79–1.49); etanercept, HR 1.12 (95% CI 0.89–1.40); golimumab, HR 0.91 (95% CI 0.59–1.39); infliximab, HR 1.03 (95% CI 0.84–1.28); rituximab, HR 1.07 (95% CI 0.74–1.55); tocilizumab, HR 1.24 (95% CI 0.71–2.17); and tofacitinib, HR 1.07 (95% CI 0.69–1.64). Secondary analyses showed similar results.

Conclusion. This multidatabase cohort study found no differences in the risk of NVFs across individual b/tsDMARDs for RA, which provides reassurance to physicians prescribing b/tsDMARDs, especially to patients at high risk of developing NVFs.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease associated with an increased risk of osteoporosis and fractures (1,2). Patients with RA have approximately 1.9 times higher incidence of osteoporosis (3) and 2.25 times higher risk of bone fracture (4) than patients without RA. However, limited comparative

data exist on the risk of nonvertebral osteoporotic fractures (NVFs) with the biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) that are commonly used for the treatment of RA. These agents are typically prescribed when remission or low disease activity is not achieved with conventional synthetic disease-modifying antirheumatic drugs. Currently, nine bDMARDs have been approved in the United States for

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SIGNIFICANCE & INNOVATIONS

- Rheumatoid arthritis (RA) increases the risk of osteoporosis and fractures. Biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) for RA may have different effects on the risk of nonvertebral osteoporotic fracture (NVF). In this multidatabase cohort study of 134,693 patients with RA, we found similar NVF risk in the new initiators of, or new switchers to, abatacept, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab, and tofacitinib compared with those on adalimumab.
- Findings were consistent across the subgroups based on sex, age, frailty levels, and prior glucocorticoid use, and osteoporotic diagnosis and medication use.
- This head-to-head comparative study of nine b/tsDMARDs for RA provides real-world evidence on the NVF risk associated with b/tsDMARDs among patients with RA, who are generally at risk of osteoporosis.

RA treatment, including tumor necrosis factor inhibitors (TNFis) (adalimumab, certolizumab, etanercept, golimumab, and infliximab), interleukin 6 inhibitors (IL-6is) (tocilizumab and sarilumab), a selective T-cell costimulation modulator (abatacept), and a CD20 inhibitor (rituximab). Additionally, three orally administered tsDMARDs—Janus kinase (JAK) inhibitors—have been approved by the US Food and Drug Administration: tofacitinib in 2012, baricitinib in 2018, and upadacitinib in 2019.

Because inflammatory cytokines, such as tumor necrosis factor, induce osteoclast maturation and suppress osteoblast activation by the Dickkopf-1 and disturb bone homeostasis (5,6), it was postulated that TNFi treatment may improve bone homeostasis in patients with RA. Small studies reported beneficial effects on bone metabolism in patients with RA treated with infliximab (7) and favorable effects on bone mineral density (BMD) levels for other TNFi agents, such as adalimumab and etanercept (8,9). Prior literature suggested a decrease in bone loss with biologic drugs, especially studies of anti-TNF blocking agents, which showed a preservation or increase in spine and hip BMD and also a better profile of bone markers (10,11). Furthermore, some small cohort studies of patients with RA reported improvements in BMD with IL-6i agents (particularly tocilizumab), possibly through an effect on inflammation, reduction in bone resorption, increase in bone formation marker, and cytokine effect on bone turnover (12,13). However, it remains unknown whether these bDMARDs improves the risk of NVFs in patients with RA.

To date, no randomized controlled trials (RCTs) of b/tsDMARDs have examined NVFs as a prespecified outcome. Few observational studies reported a lower incidence rate for vertebral fractures in patients with RA treated with TNFi versus methotrexate (14,15) but did not observe any significant differences in the risk

of nonvertebral fractures with TNFis versus non-bDMARDs (16), abatacept (17), or tocilizumab (17). However, these studies were limited by small sample size (17) and lack of evaluation of specific drugs (ie, they grouped agents to TNFi and non-bDMARD categories) (14–16). Additionally, prior evidence on the comparative NVF risk with relatively newer tsDMARD therapies is scarce. Therefore, to address this knowledge gap by providing contemporary data on the risk of NVF in patients treated with b/tsDMARDs, we sought to evaluate the comparative fracture risk with nine b/tsDMARDs using three large US health care claims databases. The primary objective of this study was to compare the incidence rate of NVFs in patients with RA initiating abatacept, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab, or tofacitinib with that in patients initiating adalimumab (common reference). The secondary objective was to evaluate this risk in patients with RA switching from a TNFi therapy to a different b/tsDMARD.

METHODS

Data sources. We used three US health care claims databases: Medicare Fee for Service (January 2008 to December 2017), Optum Clinformatics (January 2008 to March 2019), and IBM MarketScan (January 2008 to December 2017). These databases make up a large (approximately greater than 200 million patients) geographically and clinically diverse population of health insurance beneficiaries in the United States. Medicare is a federally funded program that provides health care coverage for nearly all legal residents of the United States aged 65 years and older and some disabled patients aged younger than 65 years (18). Optum and MarketScan are representative of a national commercially insured population in the United States (19–21) and contain longitudinal medical and pharmacy claims from several different managed care plans, including Medicare Advantage Plans. The Institutional Review Board of Brigham and Women's Hospital approved the study protocol and patient privacy precautions.

Study population and exposure. We identified patients aged 18 years and older with at least one inpatient visit or two outpatient visits (7–365 days apart) for RA using *International Classification of Diseases, Ninth Revision, Clinical Modification* and *International Classification of Diseases, 10th Revision, Clinical Modification* codes (22). Among these, nine mutually exclusive treatment groups of b/tsDMARDs were identified: abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab, and tofacitinib. For the primary analysis, we used an incident new-user design in which patients were required to be initiators of one of the nine medications (index treatment), with no use of any of these agents for at least 365 days before the index treatment initiation (index date). All patients were required to have continuous enrollment in the database during the baseline period of 365 days before, and including, the index date. We excluded patients with use of b/tsDMARDs other than

the exposures of interest (anakinra, baricitinib, sarilumab, secukinumab, and ustekinumab) any time before, and including, the index date and those with more than one b/tsDMARD claim on the index date. Nursing home residents and patients with malignancy were also excluded. Patients with prior hospitalization for nonvertebral fracture were also excluded because it may influence treatment choice and introduce concerns related to confounding. Patients entered the study cohorts only once, when they first met the inclusion criteria. Adalimumab was the most frequently used drug and was thus selected as a common reference.

We also conducted a secondary analysis on “new switchers” because TNFi therapies are generally considered as a first-line biologic therapy before initiation of other b/tsDMARDs in a real-world clinical setting. These new switchers were required to have used one TNFi agent without any other b/tsDMARDs in the 365 days before switching to either a second TNFi agent (adalimumab, certolizumab, etanercept, golimumab, or infliximab) or a non-TNFi agent (abatacept, rituximab, tocilizumab, or tofacitinib). The index date for this secondary cohort was defined as the date of switching.

Outcome definition. The primary outcome was a composite endpoint of NVFs, including hip fracture requiring surgery, humerus fracture requiring intervention, pelvic fracture, or wrist fracture requiring intervention. Fractures at these four anatomic sites are typically considered fragility fractures and can be accurately defined in administrative claims databases (23). We used outcome definitions that were previously validated against hospital records with high positive predictive value (greater than 92%) (23–25) and used in prior studies (16). Secondary outcomes were the individual components of the primary composite NVF endpoint.

To evaluate the impact of residual confounding and healthy adherer effect on study results, we conducted a sensitivity analysis using a negative control outcome: car crash (26). We also used herpes zoster (HZ) infection as a positive control outcome because tofacitinib is known to be associated with a nearly two-fold higher HZ risk compared with bDMARDs (27,28).

In the primary as-treated analyses, patient follow-up began on the day after the index date and ended at the first occurrence of one of the following: index therapy change (ie, switching to a different b/tsDMARD), discontinuation of the index therapy (60-day grace period and gap between prescriptions), outcome occurrence, nursing home admission, death, health plan disenrollment, or end of available data. In an intention-to-treat (ITT) model, follow-up ended at the first occurrence of one of the following: outcome, nursing home admission (because of incomplete pharmacy claims from nursing home stay), death, health plan disenrollment, end of available data, or 365 days after the index date.

Covariates. Baseline characteristics were measured on the basis of enrollment information and claims during the 365-day baseline period prior to, and including, the index date. All the covariates were known or suspected risk factors for the

outcomes of interest and used for confounding control between treatment comparisons. They included demographics, calendar time (in quarters), RA-related comorbidities, other comorbidities, and measures of health service use and preventive care, including bone mineral testing, falls, osteoporosis diagnosis, and medication use (eg, bisphosphonates, calcitonin, denosumab, raloxifene, or teriparatide), as well as prior traditional DMARD use (during all available baseline data). We also measured the claims-based frailty index (29) and combined comorbidity score (30) to account for differences in general comorbidity and frailty between the treatment comparisons (Supplementary Tables 1 and 2).

Statistical analysis. To account for the nonrandom allocation of patients to the treatment groups, we used a propensity score (PS)-based stabilized inverse probability of treatment (IPT) weighting approach, with the average treatment effect on the treated to adjust for more than 70 baseline covariates within each database (31,32). PSs were calculated by using a multinomial logistic regression that modeled the probability of initiating each of the eight b/tsDMARDs versus adalimumab. The index therapy was the dependent variable, whereas all the confounders were independent variables in the PS models. IPT weights were calculated as the inverse of patients' estimated probability of treatment, and weights were stabilized and truncated at 0.5 and 99.5 percentiles of overall weights to limit variance inflation (33).

We report incidence rates (IRs) per 1000 person-years for all outcomes within each database as well as pooled across three databases. For each drug comparison, adjusted hazard ratios (HRs) were estimated by using weighted Cox proportional hazards models, and 95% confidence intervals (CIs) were calculated by using robust variance estimators within each database. We further adjusted for covariates with an imbalance of standardized difference greater than 10% after PS weighting (34). To obtain the pooled estimates from three databases, Cox proportional hazards models stratifying by database were used.

We conducted prespecified subgroup analyses for the primary composite NVF endpoint by sex (male or female), frailty category (pre-frail, frail, severely frail), baseline use of glucocorticoids (yes or no), and baseline osteoporotic diagnosis or medication use (yes or no).

All analyses were performed by using SAS 9.4 (SAS Institute, Inc.).

RESULTS

Study cohort and patient characteristics. For the primary new-user cohort, we identified a total of 134,693 b/tsDMARD initiators with RA after applying all the inclusion/exclusion criteria across the three databases (abatacept, $n = 13,753$; adalimumab, $n = 35,305$; certolizumab, $n = 7864$; etanercept, $n = 34,661$; golimumab, $n = 6836$; infliximab, $n = 21,408$; rituximab, $n = 7195$; tocilizumab, $n = 3499$; and tofacitinib, $n = 4172$). The mean age was 72 years in the Medicare database, 54 in the Optum database, and 52 in the MarketScan database (Supplementary Table 1). During

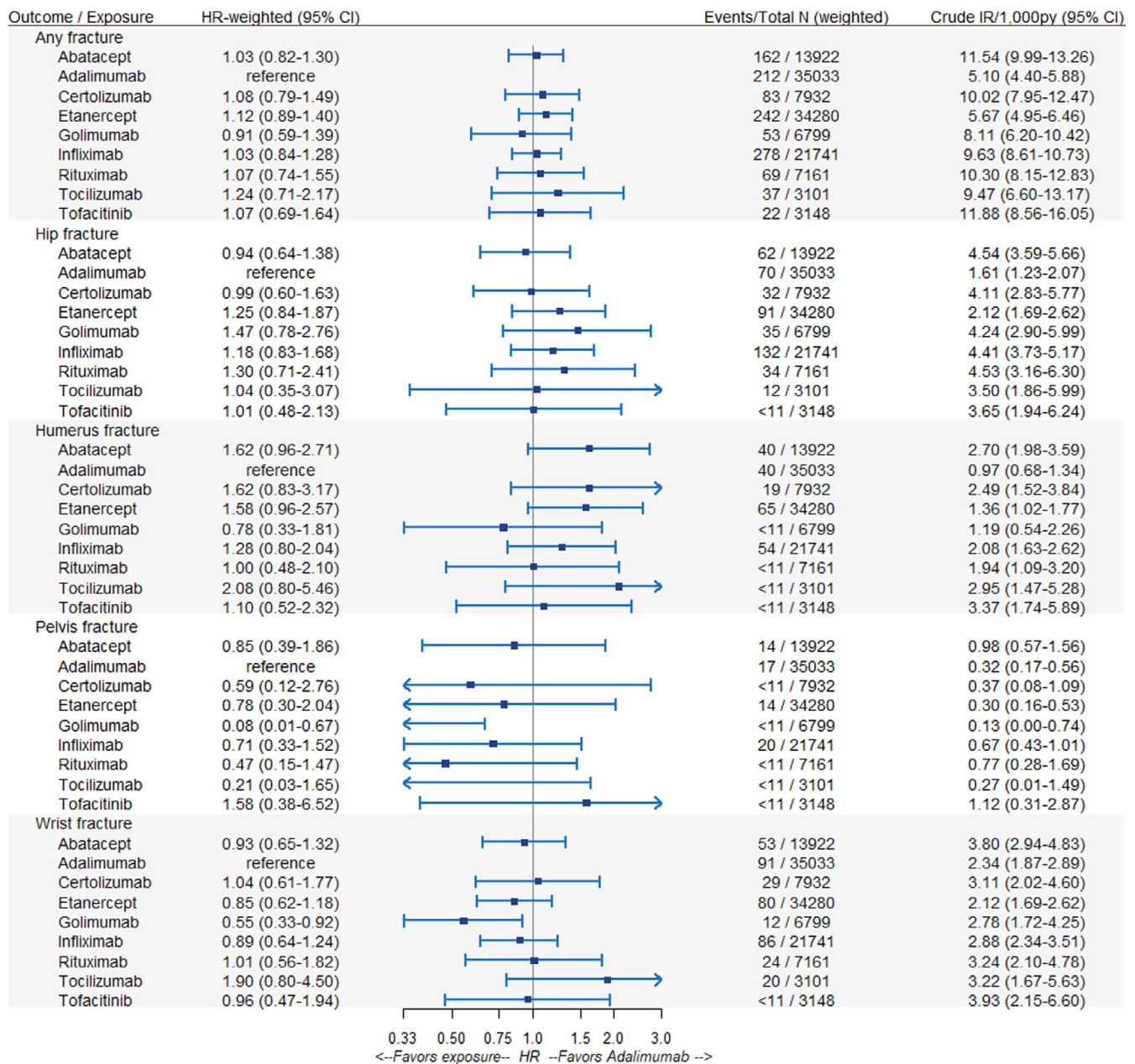


Figure 1. Forest plot for the primary analyses—number of events, number of patients, incidence rates (IRs), and hazard ratios (HRs) for nonvertebral fracture endpoints in eight biologic and targeted synthetic disease-modifying antirheumatic drugs versus adalimumab—pooled across three databases: as-treated propensity score–based inverse probability of treatment weighting analyses in new-user cohorts. CI, confidence interval; py, person-years. [Color figure can be viewed at wileyonlinelibrary.com]

the 365-day baseline period, 39% to 65% of patients used methotrexate, 64% to 71% used corticosteroids, and 13% to 30% had osteoporosis. After PS weighting, most of the covariates were well balanced for all comparisons in the three databases, with the standardized difference less than 10% (35,36) (Supplementary Table 2).

Risk of NVF. In the primary new-user cohort, a total of 1234 crude composite NVF events occurred for the primary as-treated analysis across the three databases during 158,027 person-years across nine treatment groups (IR per 1000 person-years 7.81; 95%

CI 7.38-8.26). Among the individual components of the composite NVF outcome, the IR per 1000 person-years was highest for hip fractures (3.14 [95% CI 2.87-3.43]; $n = 499$), followed by wrist (2.72 [95% CI 2.47-2.99]; $n = 432$) and humerus fractures (1.73 [95% CI 1.53-1.95]; $n = 275$), whereas it was lowest for pelvis fractures (0.50 [95% CI 0.39-0.62]; $n = 79$). Among adalimumab initiators, 189 NVF crude events occurred over 37,087 person-years (Figure 1). The mean follow-up time (days) in the as-treated analysis was 428 days (SD 462) and ranged from 384 (Optum) to 490 days (Medicare).

The crude IR per 1000 person-years for the primary composite NVF endpoint in adalimumab initiators was 5.10 (95% CI 4.40-5.88), whereas for exposure groups, it ranged from 5.67 (95% CI 4.95-6.46) in etanercept to 11.88 (95% CI 8.56-16.05) in tofacitinib initiators (Figure 1).

The adjusted PS-weighted HRs for the risk of a composite NVF outcome in all b/tsDMARD exposures compared with adalimumab were as follows: abatacept, HR 1.03 (95% CI 0.82-1.30); certolizumab, HR 1.08 (95% CI 0.79-1.49); etanercept, HR 1.12 (95% CI 0.89-1.40); golimumab, HR 0.91 (95% CI 0.59-1.39); infliximab, HR 1.03 (95% CI 0.84-1.28); rituximab, HR 1.07 (95%

CI 0.74-1.55); tocilizumab, HR 1.24 (95% CI 0.71-2.17); and tofacitinib, HR 1.07 (95% CI 0.69-1.64) (Figure 1). In the secondary outcome analyses, the point estimates were consistent, with no significantly elevated risk of hip, humerus, pelvis, or wrist fracture for b/tsDMARDs versus adalimumab, with the exception of a lower risk of wrist fracture observed in the initiators of golimumab than in the initiators of adalimumab (HR 0.55; 95% CI 0.33-0.92) (Figure 1).

We observed a higher number of NVF events in patients aged 65 years and older enrolled in the Medicare database than in younger patients from commercial databases; however, the point estimates were similar in younger and older patients (Figure 2).

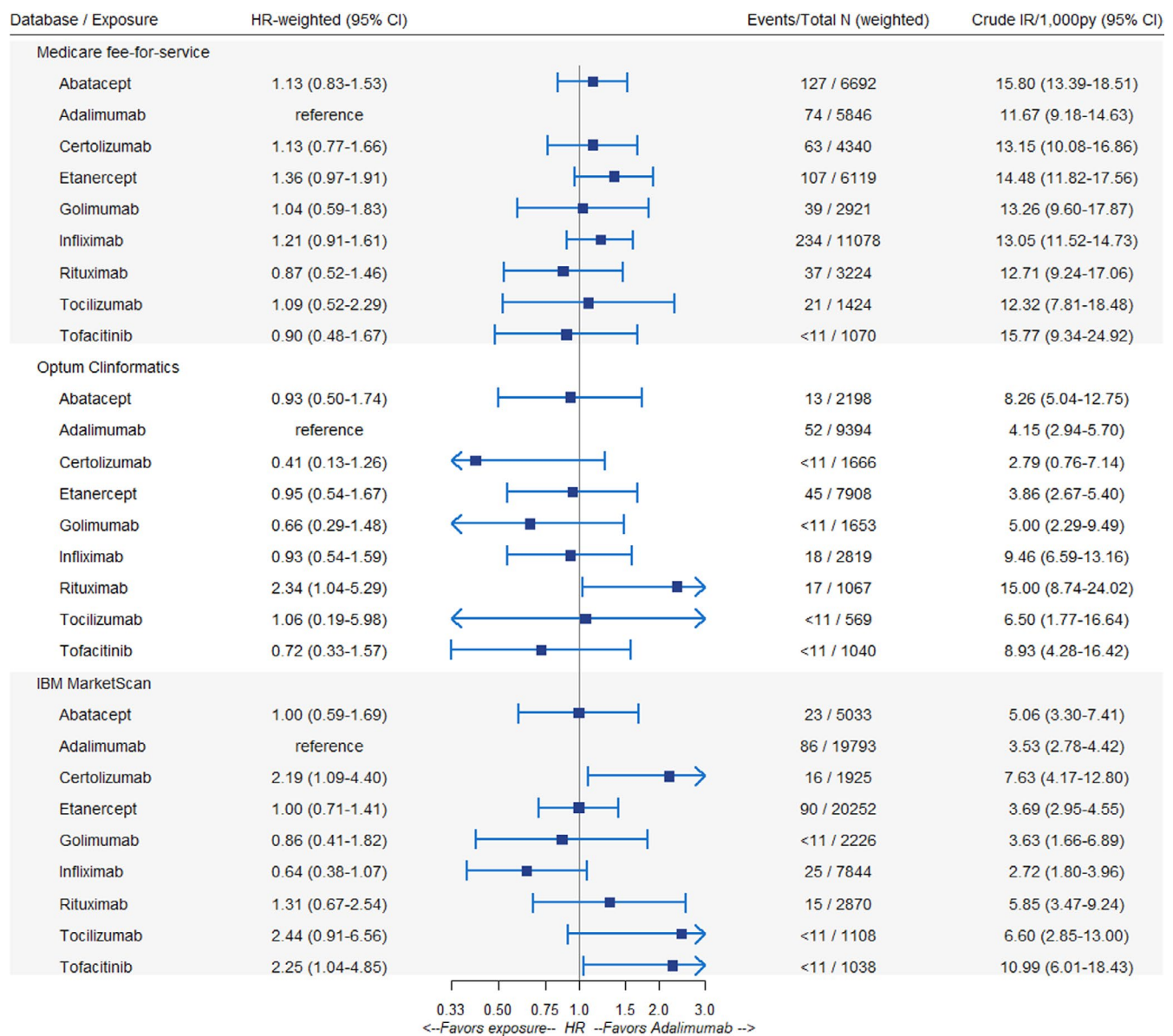


Figure 2. Forest plot by data source—number of events, number of patients, incidence rates (IRs) and hazard ratios (HRs) for the primary nonvertebral fracture endpoint in eight biologic and targeted synthetic disease-modifying antirheumatic drugs versus adalimumab—pooled across three databases: as-treated propensity score-based inverse probability of treatment weighting analysis in new-user cohorts. CI, confidence interval; py, person-years. [Color figure can be viewed at wileyonlinelibrary.com]

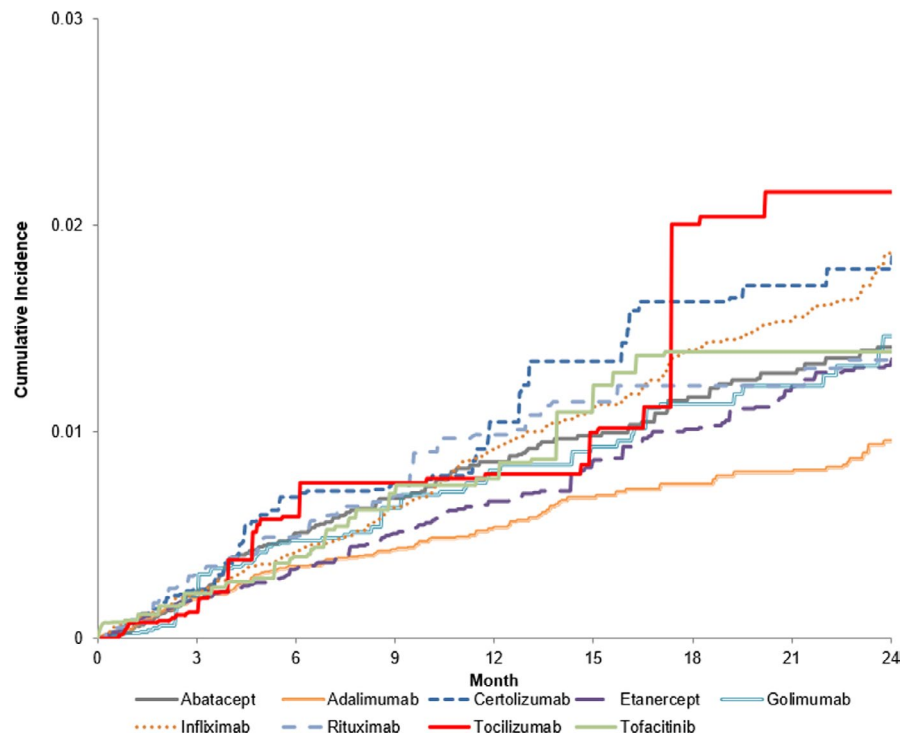


Figure 3. Cumulative incidence plot pooled across three databases for the primary nonvertebral fracture endpoint in eight biologic and targeted synthetic disease-modifying antirheumatic drugs versus adalimumab in the propensity score-weighted population. [Color figure can be viewed at wileyonlinelibrary.com]

PS-weighted cumulative incidence plots showed findings consistent with these results (Figure 3).

Sensitivity analyses. The results were also consistent for the secondary analyses of ITT (Supplementary Figure 1). We observed a null finding for the negative control outcome of car crashes across eight b/tsDMARDs versus adalimumab, as expected (Supplementary Figure 2). In terms of positive control outcome of HZ infection, we reproduced the twofold higher risk with tofacitinib versus adalimumab initiation (HR 2.13; 95% CI 1.68-2.69).

Subgroup analyses. Results were consistent for the composite NVF endpoint among subgroups based on sex, frailty, baseline use of glucocorticoids, and baseline osteoporotic diagnosis and medication use (Supplementary Figure 3). We noticed higher IRs in patients from the Medicare database, as their mean age was higher than that of patients from the commercial database, as well as in patients with severe frailty and baseline use of glucocorticoids.

Secondary analyses. For the secondary cohort of new switchers with prior use of a TNFi medication, we identified 42,688 patients with RA switching to one of the nine b/tsDMARDs. The IR per 1000 person-years (95% CI) for the composite NVF outcome in this population was slightly higher (8.22; 7.43-9.08) compared with that in the primary new-user

cohort because these patients may be at a more advanced stage of RA. However, the results from this secondary analysis were consistent with the primary analyses of the new-user cohort (Supplementary Figure 4).

DISCUSSION

In this large multidatabase cohort of 134,693 patients with RA initiating one of the nine b/tsDMARDs, the risk of NVFs was similar for abatacept, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab, and tofacitinib compared with adalimumab. The risk for secondary outcomes, including hip, humerus, pelvis, and wrist fractures, was also not different between the new users of these eight b/tsDMARD exposure groups versus the adalimumab group, except the lower risk of wrist fracture observed in the initiators of golimumab than observed in the initiators of adalimumab, which could be due to the random chance or small number of events. Consistent findings were observed in the secondary analyses evaluating NVF risk among patients with RA switching from a TNFi to a different b/tsDMARD. We also observed a null finding for the negative control outcome of car crashes and a higher HZ infection risk with tofacitinib. Results were also similar in the sensitivity and subgroup analyses. Although NVF events occurred more frequently in older Medicare patients than in patients in the other two databases, the comparative NVF risk associated with eight b/tsDMARD exposure groups versus adalimumab was not different across age groups. The IRs observed in our analyses for both the

primary composite NVF end point and secondary endpoints were similar to findings of prior real-world studies comparing DMARDs for this risk (14–17).

Fracture is a common adverse event in patients with RA because they are at higher risk of developing osteoporosis and fractures (1,2). A meta-analysis of 13 studies showed an elevated risk of bone fracture in patients with RA than patients without RA (risk ratio 2.25; 95% CI 1.76–2.87) (4). This risk may further increase with age, frailty, and commonly used medications (such as opioids and selective serotonin reuptake inhibitors) (14) in patients with RA. However, the evidence on the influence of bDMARD use on fracture risk in patients with RA is conflicting (14–17), whereas evidence on tsDMARDs is scarce. Few studies evaluated the comparative risk of vertebral fractures in patients with RA (14,15). The North American Consortium of Rheumatology Researchers of North America (CORRONA) registry study with 8419 female patients with RA and the longitudinal prospective observational study using the FORWARD registry in the United States found a reduced risk for vertebral fractures in the TNFi group compared with the methotrexate group (14,15). However, these beneficial effects with TNFi agents were not observed in terms of nonvertebral fractures (16,17). Our findings are consistent with such prior studies evaluating the risk of NVFs. The analyses from the previously mentioned FORWARD study did not find any differences in the NVF risk for TNFi (HR 0.93; 95% CI 0.86–1.25) and non-TNFi bDMARDs (HR 1.04; 95% CI 0.70–1.53) versus methotrexate monotherapy (14). Similar to our results, another population-based cohort study of 47,034 patients with RA also observed no difference in the risk of NVFs with TNFis (HR 1.07; 95% CI 0.57–1.98) compared with non-bDMARDs (16). Along the same lines, an observational study using the Korea National Health Insurance Service data sets did not find significant differences in the risk of NVFs between patients with RA receiving TNFis and those receiving abatacept (HR 1.06; 95% CI 0.43–2.59) or tocilizumab (HR 1.18; 95% CI 0.47–3.00) (17). The consistency of our findings with these prior study results is reassuring, as our larger sample size allowed us to evaluate the individual components of the NVF endpoint, which showed similar results. Furthermore, because prior studies typically grouped TNFi or non-TNFi agents into a single category, the comprehensive comparative assessment of individual medications for NVF risk was not done before (14–17). Additionally, the data on NVF risk with IL-6 inhibitors and tsDMARDs were limited. Among the IL-6 inhibitors, tocilizumab treatment was shown to stabilize BMD levels in patients with RA (37). Of the tsDMARD agents, tofacitinib was found to preserve cortical trabecular hardness in rats (38,39). However, the impact of these osteoprotective benefits on NVF outcomes in comparative assessment with other agents was lacking thus far. Our findings suggest no difference in the NVF risk for agents from these drug classes (ie, tocilizumab and tofacitinib) compared with adalimumab.

Our study used routinely collected data, representing the actual RA clinical setting; thus, the evidence is valuable because it

is not feasible to conduct RCTs with head-to-head comparison of all b/tsDMARDs for the comprehensive assessment of fractures. Our results are clinically meaningful because they will help rheumatologists who are concerned about the risk of fractures make an appropriate treatment choice in patients with RA, particularly for those at a higher risk of NVFs. The choice of DMARD medication in patients with RA is typically based on their efficacy, economic aspects, patients' preferences, routes of administration, and safety concerns (40–42). In this study, we were able to conclude that b/tsDMARD agents are not different in terms of risk of hip, humerus, pelvis, and wrist fractures.

This study has several strengths and clinical implications. This is the first comprehensive evaluation of nine b/tsDMARD agents for NVF risk in a real-world clinical setting. Our findings will be useful in making an evidence-based treatment choice between different DMARDs. Another strength was the generalizability to the large proportion of patients with RA because we used three national US insurance claims databases, including Medicare data, representing the older population rarely studied in clinical trials, and Optum and MarketScan data sources, representing primarily the working population and their dependents. Furthermore, the secondary analyses on new switchers improved generalizability and allowed us to mimic actual clinical practice for RA because it represented a large proportion of patients with RA who used TNFi agents before switching to non-TNFi b/tsDMARDs. Our large sample size also allowed us to achieve an adequate study size for the comparison, with relatively newer agents from the class of IL-6 inhibitors (tocilizumab) and JAK inhibitors (tofacitinib), and to evaluate the risk of less commonly studied specific NVFs. To minimize confounding by indication, we used rigorous pharmacoepidemiologic approaches, including the new-user design, active comparators, and PS-based IPT weighting (43,44). We used validated outcome definitions, were also able to produce the null finding in the analyses focusing on the negative control outcome, and were able to reproduce the higher risk of HZ infections with tofacitinib and adalimumab, suggesting minimal residual confounding. We conducted analyses separately in each database to achieve optimal confounding control given the known differences in demographics and other patient characteristics across the databases. We provided relative risks (ie, HR) as well as absolute risk of NVFs and several specific NVFs across all comparisons. Lastly, our sensitivity and subgroup analyses showed consistent results.

This study has a few limitations. First, residual confounding is possible even though we adjusted for more than 70 variables potentially related to NVF risks using PS weighting, including claims-based frailty score and prior osteoporosis diagnosis and medication use. Second, the health care claims databases that we used did not offer information on body mass index, diet, physical activity, calcium/vitamin D intake, or RA duration or severity. However, we used proxy variables to reduce confounding due to those differences. Third, outcome misclassification cannot be ruled out because we relied on diagnosis codes for identifying

endpoints, but we used validated endpoints that required diagnosis codes accompanied by procedure codes (except pelvic fractures). Fourth, the vertebral fracture endpoint could not be evaluated because it is difficult to capture incident cases in the claims database. We did not include more recently approved drugs, such as sarilumab, baricitinib, or upadacitinib, in our investigation because of a low number of patients using these medications in our data sources. Analyses specific to dose or route of administration were also not conducted. Lastly, the mean follow-up for as-treated analyses (ie, time on treatment) was short (less than 1.2 years); however, 16% of patients had more than 2 years and 8% of patients had more than 3 years of follow-up.

In conclusion, this large multidatabase real-world study of 134,693 patients with RA initiating b/tsDMARDs provides comprehensive assessment of risk of NVFs across nine different agents. We found no significant differences in the risk of NVF in the new users of or new switchers to eight b/tsDMARDs compared with adalimumab. These findings may be reassuring to physicians prescribing b/tsDMARDs to patients with RA, particularly those at the higher risk of NVFs.

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Data may be obtained from a third party and are not publicly available.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Pawar and Kim had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Pawar, Desai, Kim.

Acquisition of data. Pawar, Desai, He, Bessette, Kim.

Analysis and interpretation of data. Pawar, Desai, He, Bessette, Kim.

ROLE OF THE STUDY SPONSOR

Bristol-Myers Squibb was given the opportunity to make nonbinding comments on a draft of the paper. The authors independently collected and analyzed the data, interpreted the results, determined the final wording, and had the final decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Bristol-Myers Squibb.

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